

ANNUAL REVIEW OF PHYSIOLOGY

EDITORIAL COMMITTEE

J. F. FULTON

M. H. JACOBS

F. C. MANN

R. F. PITTS

M. B. VISSCHER

# ANNUAL REVIEW OF PHYSIOLOGY

VICTOR E. HALL, *Editor*

*Stanford University*

JEFFERSON M. CRISMON, *Associate Editor*

*Stanford University*

ARTHUR C. GIESE, *Associate Editor*

*Stanford University*

VOLUME XII

1950

PUBLISHED BY  
ANNUAL REVIEWS, INC.  
AND THE  
AMERICAN PHYSIOLOGICAL SOCIETY

---

ON SALE BY  
ANNUAL REVIEWS, INC.  
STANFORD, CALIFORNIA, U.S.A.

Med  
CVR

543229

QPI  
.A52

ANNUAL REVIEWS, INC.  
STANFORD, CALIFORNIA, U.S.A.

---

FOREIGN AGENCIES

*London:*

H. K. LEWIS & COMPANY, LIMITED  
136 GOWER STREET, LONDON, W. C. 1

*Moscow:*

MEZHDUNARODNAYA KNIGA  
KUZNETSKY MOST, 18

*The Hague:*

MARTINUS NIJHOFF  
9, LANGE VOORHOUT

PRINTED AND BOUND IN THE UNITED STATES OF AMERICA BY  
GEORGE BANTA PUBLISHING COMPANY

P

0-5-0-5-0

## PREFACE

In this volume we present the first of a series of prefatory chapters to the *Annual Review*. It is our intention to invite outstanding leaders of our profession to step for a moment outside their field of specialization and to survey some general aspect of the development and present status of physiology from the vantage point of their maturity and wisdom. If the experience of several years makes this departure seem profitable, it will be made a permanent feature of the *Review*. We are particularly indebted to Dr. Eugene F. Dubois who prepared at short notice the delightful and illuminating survey of "Fifty Years of Physiology in America" with which this series is inaugurated.

The present volume is also notable in that all the authors who accepted our invitation to contribute have been able to complete their tasks. This is evidence of restoration, after the dislocations of the past decade, of a steady state in which physiologists can again make commitments several years in advance with some confidence of being able to meet them.

Our thanks must again be expressed to our contributors for the time and effort they have so generously donated, to our publishers, the George Banta Company, for their continuing co-operation, and to our editorial assistants, Barbara Darneal, Marjorie Ehrhard, Joyce Fairweather, Carol Kupke, and Virginia Lee, whose loyal and efficient service should not be hidden in anonymity.

J.F.F.	M.B.V.
M.H.J.	J.M.C.
F.C.M.	A.C.G.
R.F.P.	V.E.H.

TOPICS AND AUTHORS  
ANNUAL REVIEW OF PHYSIOLOGY  
VOLUME XIII (1951)

Permeability, H. B. Steinbach  
Radiant Energy, H. J. Curtis  
Bioelectric Phenomena, O. H. Schmitt  
Developmental Physiology, J. Runnström and T. Gustafsson  
Physiological Effects of Heat and Cold, R. Grant  
Water Balance, J. Govaert  
Muscle, A. V. Hill and D. K. Hill  
Digestive System, E. S. Nasset  
Liver, J. W. Wilson  
Peripheral Circulation, K. G. Wakim  
Heart, H. B. Burchell  
Respiration, J. S. Gray and F. S. Grodins  
Blood (Volume), M. I. Gregersen  
Kidney, E. E. Selkurt  
Conduction and Transmission in the Nervous System, T. H. Bullock  
Somatic Functions of the Nervous System, G. Moruzzi  
Visceral Functions of the Nervous System, N. E. Freeman and R. S. Gilfillan  
Electrical Activity of the Brain, H. Gastaut  
Metabolic Functions of the Endocrines, J. A. Russell  
Reproduction, J. E. Markee

## CONTENTS

	PAGE
PREFATORY CHAPTER, <i>E. F. DuBois</i> . . . . .	1
PHYSICAL PROPERTIES OF PROTOPLASM, <i>M. J. Kopac</i> . . . . .	7
RADIANT ENERGY, <i>A. Edelmann</i> . . . . .	27
PHYSIOLOGICAL GENETICS, <i>D. G. Catcheside</i> . . . . .	47
GROWTH, <i>P. C. Zamecnik and J. C. Aub</i> . . . . .	71
THE PHYSIOLOGY OF SUPPORTING TISSUE, <i>M. J. Dallemagne</i>	101
PHYSIOLOGICAL RESPONSES TO HEAT AND COLD, <i>J. D. Hardy</i>	119
WATER METABOLISM, <i>J. R. Elkinton</i> . . . . .	145
RESPIRATORY SYSTEM, <i>W. O. Fenn, H. Rahn, and A. B. Otis</i>	179
DIGESTIVE SYSTEM, <i>M. I. Grossman</i> . . . . .	205
THE COAGULATION OF BLOOD AND HEMOSTASIS, <i>A. J. Quick</i>	237
BLOOD GAS TRANSPORT, <i>R. C. Darling</i> . . . . .	265
ENERGY METABOLISM, <i>W. H. Chambers and W. H. Summer-</i> <i>son</i> . . . . .	289
THE PERIPHERAL CIRCULATION, <i>O. G. Edholm</i> . . . . .	311
HEART, <i>A. Hemingway</i> . . . . .	345
KIDNEY, <i>J. Trueta</i> . . . . .	369
CONDUCTION AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM, <i>H. A. Blair</i> . . . . .	399
SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM, <i>A. A. Ward,</i> <i>Jr.</i> . . . .	421
VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM, <i>R. B. Liv-</i> <i>ingston</i> . . . . .	445
PHYSIOLOGY OF SMELL AND TASTE, <i>H. D. Patton.</i> . . . .	469
PHYSIOLOGY OF VISION, <i>R. Granit</i> . . . . .	485
METABOLIC FUNCTIONS OF THE ENDOCRINE GLANDS, <i>J. Tep-</i> <i>perman and H. M. Tepperman</i> . . . . .	503
REPRODUCTION, <i>S. A. Asdell</i> . . . . .	537
INDEXES . . . . .	557

ANNUAL REVIEWS, INC., and the Editors  
of its publications assume no responsibility  
for the statements expressed by  
the contributors to this *Review*.

PREFATORY CHAPTER  
FIFTY YEARS OF PHYSIOLOGY IN AMERICA  
A LETTER TO THE EDITOR

BY EUGENE F. DuBOIS

*The Russell Sage Institute of Pathology, affiliated with the New York Hospital,  
The Department of Physiology, Cornell University Medical College,  
New York, N. Y.*

TO THE EDITOR OF THE ANNUAL REVIEW OF PHYSIOLOGY:

In your letter of June 15, 1949 you extend to me the tempting invitation to write a prefatory chapter for Volume XII which will appear in 1950. In your letter you say:

This is an invitation, the motive behind which is our desire to make the Review something more than a consideration in detail of the current advances in our science. Physiology is a form of human activity as well as an accumulation of knowledge. As such it has a history of hopes, ambitions, enthusiasms, fashions and phobias. Older members of the profession are retiring, newer ones rising to prominence. New institutions are being founded, older ones changing their form and function. New patterns of financial support, of teaching and research are emerging with various influences on their conduct. The economic position of the members of the professions relative to that of other callings alters, creating problems of adequate staffing of laboratories. Interest in the philosophic basis of science is increasing as we attempt to approach our ultimate task, the revealing of the nature of man.

Your request is a serious challenge, and I would not dare to attempt a chapter in the short time available were it not for the implication that in subsequent years other physiologists would be called upon to fill the many gaps. All that I can do at the present time is to write from a very personal viewpoint. What one should do as a reviewer is to go over the whole history of physiology of the last fifty years and try to be impersonal. The delightful *History of The American Physiological Society Semicentennial*, published in 1938, takes care of North America, but has relatively little to say about the development of physiology as a whole. In the first two decades of this century, we received most of our inspiration from the other side of the Atlantic and now we note with joy the resurgence of physiology in Europe.

If I were to review physiology in the last fifty years, I would first sketch the history of our discipline, then contrast the old situation with the recent, and finally attempt to predict the direc-

tion in which we are travelling. This last would require prophecy by means of extrapolation, a procedure that is most hazardous in the Year of Our Lord, 1949.

Every writer on this subject has his own viewpoint, and it is quite important that the reader should understand this limitation. My own viewpoint is that of a man trained first in medicine, then diverted into pathology, pathological physiology, physiology, nutrition, private practice, academic medicine, military medicine, and finally into the teaching of physiology to medical students. Most of the time has been spent in New York, with three periods of study in Germany. In all of these fields and in all places, the dominant feature has been physiology. It is physiology which binds together the medical sciences.

Perhaps I am stretching things a bit when I try to extend my personal observations back to the beginning of this century. My vivid memory of a brief period as an orderly in a fever hospital at the end of the Spanish-American War indicates that physiology was quite unknown in military medicine at that time. My college courses in zoology and botany in 1900 were likewise devoid of physiology. My medical school course in physiology in 1903 consisted of dry lectures and distant demonstrations of a few animal experiments. Biochemistry and pharmacology, which even then were separate courses, added but little light. This was in one of the so-called better medical schools. There must have been a few schools in the country with more inspired teachers.

In the period between 1906 and 1910 in New York and throughout our country, there was a growing wave of enthusiasm for research in physiology as applied to medicine. Up to that time a young medical man who wished to make an academic career in internal medicine concentrated on pathology, as had his predecessors from the time of Laënnec down to Osler. Now, under the influence of a group of enthusiasts, the young men were encouraged to study biochemistry and physiology and apply their methods to clinical problems. There was a great appreciation of Ludolf Krehl's book on pathological physiology. Rather suddenly, it was realized that disease furnished the physiologist with human material much more dramatic than that obtained in animal experiments. After 1910 there was an ever increasing collaboration between the clinical investigator, the physiologist, the biochemist, and the pharmacologist.

I believe it was Starling who said, "Physiology of today is the medicine of tomorrow." Nowadays we may have to admit that the

medicine of today is the physiology of tomorrow. Take, for example, the discovery of insulin or the pioneer studies of Cushing on the pituitary. In the first decade of this century, there were relatively few strong departments of physiology in this country. It was almost necessary to go abroad for study. General physiology was beginning to appear on the horizon. Biochemistry was taking over more and more sections of what had been considered physiology. Histology had split off and returned to anatomy. Nutrition was growing up as an important part of physiology. Biophysics as a term had not made its appearance in 1910, but was taken for granted as an integral component of physiology.

Physiology as a science was developing well in the period before World War I. The war itself, as we look back on it now, demonstrated that the military authorities and the country as a whole had little appreciation of the help that could be obtained from physiologists. It is true that the urgent necessities of gas warfare demanded intensive work by chemists, biochemists, and pharmacologists. Physiologists contributed a little in the way of gas masks and a small amount of research in aviation, submarine medicine, and practical nutrition.

In World War I, there was nothing like the eager demand for research that characterized World War II. It so happened that I served in the Research Division of the Navy's Bureau of Medicine and Surgery in both wars. At the end of World War I, the Division consisted of two junior officers and two enlisted men. Early in World War II the Division occupied a whole building; there was an Admiral in charge and about eight other senior officers.

Between the two wars, departments of physiology in America increased in size and strength. European laboratories had been hit so hard that we had to train our own younger generation, though European contacts were still extremely valuable. This was a period of developing support for research from private foundations. The military authorities did not foresee the aid from research, and they maintained but little contact with physiologists.

The psychologists had rather a rough reception in World War I, but between wars they pulled themselves together and began to take over some fields of research that formerly seemed to belong to physiology. Apparently there is no clear division between psychology and physiology and probably no need for one. Be that as it may, the psychologists are now making great advances in the field of human engineering and are studying the "physiology" of

machines and tasks as well as of the men concerned in operating them. After all, a piece of apparatus such as the cockpit of an aeroplane is nothing more than an extension of a man's nervous system.

It was the impact of World War II that brought, not only to the military authorities, but also to the citizens at large, a full realization of the possibilities of research. Machines such as aeroplanes, tanks, guns, and radar were rapidly developed beyond the limit of contemporary human capabilities. There was a frantic search for an extension of these capabilities. Physiological limits were explored and actually extended, though not nearly enough to satisfy the engineers.

During the war the heads of university departments spent most of their time in Washington or in laboratory work helping Washington. The effect on science was not as bad as might have been expected. There was active exchange of ideas. The many scientific conferences were of the highest order. Many new and unsuspected problems were uncovered. Mimeographed reports were issued by the thousands, and now, fortunately, the results in greatly condensed form are recorded in the literature.

Research has been appreciated to such an extent that it has become embarrassing. The public expects every problem to be solved by the expenditure of enough money. The grants for projects by government agencies are of extraordinary liberality and are well screened and managed. As a result, laboratories in all fields are expanding faster than the supply of trained personnel. Unfortunately, the greatest expansion came at the very time when the shortage was most acute on account of the interruption of training during the war. Government support of research could be most helpful if there were assurance of continuity as well as wise management. A wave of economy on the part of Congress would mean that hundreds of investigators and technicians would be scrambling for new jobs. There would be a drastic reduction in all budgets.

At the present writing, physiology in the United States has expanded until it somewhat resembles an acromegalic giant. At the recent meeting at Detroit, there were 503 papers on physiology. There are now 999 active members of the American Physiological Society. Is the situation better than it was in the old days when the whole Society could meet in one small room?

The world has changed, and we cannot turn back the clock. Nevertheless, we can study the best aspects of the old system and try to recapture some of them. As I remember the departments

of physiology in the first two decades of this century, they were small and compact. There were few technicians. The professor spent the day making his own physical measurements and chemical analyses. Then he went home, and a maid cooked the dinner and washed the dishes. Nowadays, it is the technician who makes the scientific measurements, and the professor washes the dishes after the dinner that has been cooked by his wife.

It is interesting to see the modern pattern of applications for government grants of projects in the field of physiology. Young investigators, a few years after receiving the Ph.D., expect the aid of an electronics technician, a biochemist, and an animal caretaker; and they all seem to need at least one piece of apparatus that costs two thousand dollars. When this mountain goes into labor, let us hope that there will issue forth at least one mouse. Who knows? Instead of a mouse, it may be the cure for cancer.

In the first two decades, support of teaching and research came from the modest budget of the university, but each dollar so secured was flexible. Like the normal red blood cell, it could squeeze itself through narrow capillaries and could turn sharp corners. The dollar from most of the modern research projects is rigid, like a red blood cell preserved with formalin. The old dollar from a well balanced budget was worth 100 cents. The new dollar in a distorted departmental budget is worth only a fraction of that amount.

In the early days, the head of a department had one vexatious week when he tried to wrangle a better budget from his dean. Now he has to worry all year about old and new projects. In the old days he belonged to two or three committees and two or three scientific societies. Now he has accumulated three or four times this number and has to make innumerable trips to Washington where, indeed, his services are greatly needed. In the old days his department was so small that he could follow in detail the work of his assistants. Now he has less time for a larger staff.

On the brighter side of the picture we see, every year, more and more young men and women sincerely anxious to make a career in physiology. They are better trained in fundamentals than their predecessors. They are carried along in the enthusiasm of a rapidly advancing front of knowledge. They have many more opportunities for prolonged training. Where will this training take them in the field of physiology? What is the field of physiology? Physiology in the past has included histology, psychology, pharmacology, biochemistry, biophysics, nutrition, general physiology, pathological physiology, and many other subdivisions. It still contains parts of

all of these, even though most of their material has been transferred to other departments for reasons of academic administration and teaching. Physiology in a medical school is centered around man but has no sharp boundaries. Perhaps medical school physiology may be considered as comprising the material found in most of the large textbooks of physiology.

It is with a certain amount of regret that physiologists see large proportions of their old fields split off into new departments. What concerns them most at the present time is the proposal to form departments of biophysics. If this were done in the strict sense of biophysics, there would be nothing left since there is hardly anything in physiology that is not either biochemistry or biophysics.<sup>1</sup> Most of the people who call themselves biophysicists concentrate their attention on radiation in the region of x-rays. There is one text book of "biophysics" that does not even mention the words "heat" and "calorie." Apparently "biophysics" does not extend into the longer wave lengths of radiation. If they want to split off such highly technical and difficult subjects as the atomic bomb effects and x-rays, that is one thing; but if they split off optics, hemodynamics, respiration, and heat regulation, it is an entirely different matter.

Perhaps physiology could stand another large split. It is tough and grows with pruning. There will surely remain its fundamental task of pulling together all the various parts of the medical school curriculum. This must be clearly recognized. Every year in an introductory lecture, I try to show the first year medical students the place in their studies that is occupied by physiology. I start off by drawing overlapping circles representing physics, chemistry, and biology. On top of these and again overlapping come the circles for anatomy, biochemistry, and the other preclinical studies. Then comes a top overlapping layer of the clinical studies in medicine, surgery, etc. Finally, superimposed over most of the diagram comes an oblong "Physiology" in red chalk, including parts of all the curriculum. Physiology has no limitations in any discipline that deals with living matter. The more that physiology invades anatomy, clinical medicine, and all the other departments, the better it becomes for science as a whole. It is not the title that makes the physiologist, it is the point of view, the mode of thought.

<sup>1</sup> An illustration in point is the title of that excellent publication *Journal of Applied Physiology*. Logically we should now change the title of its parent to *American Journal of Non-Applied Physiology*. Carrying this logic a little farther, one would arrive at the definition: Non-applied, non-biochemical, non-biophysical, non-etc.-physiology = Physiology.

# PHYSICAL PROPERTIES OF PROTOPLASM<sup>1</sup>

BY M. J. KOPAC

*Department of Biology, Washington Square College of Arts and  
Science and the Graduate School of Arts and Science  
New York University, New York 3, New York*

Studies that have shown considerable progress are in permeability, nucleocytoplasmic interrelations, and the fractionation of subcellular particulates. The more significant contributions to our knowledge of protoplasm are concerned with ultrastructure, especially of sol-gel phenomena. It was impossible to include all papers, numbering well over 400, that were published on these topics during the past two years. The literature cited does, however, provide a key to most of the papers.

## PHYSICAL CHARACTERISTICS

*Transmission of ultraviolet light.*—Brumberg & Larinow (1) reported that the cytoplasm of living fibroblasts absorbed more light at 254 to 275  $m\mu$  than the nuclei. After the cells were killed, cytoplasmic absorption decreased while that of the nucleus increased. Following 2 min. exposure to unfiltered ultraviolet, for example, the nucleus, nuclear membrane, and nucleolus absorbed radiation more intensely than the cytoplasm. Photographs of living chick fibroblasts taken at 253  $m\mu$  also showed considerable absorption by the cytoplasm which decreased after the same cells were killed [Ris & Mirsky (2)]. Ely & Ross (3), however, claimed that grasshopper spermatocyte chromosomes absorbed light at 257  $m\mu$  even while the cells were in mitosis [see also Ludford *et al.* (4)].

The absorption properties of nucleic acids in living cells may very well differ from those in dead cells. Commoner (5) and Commoner & Lipkin (6) competently discussed the problems of ultraviolet absorption by cell structures containing nucleic acids. Such nucleic acids may exist as oriented aggregates thereby eliciting absorption anomalies. The extinction values at 257 to 260  $m\mu$  depend on the following: (a) Where all or part of the nucleic acid is oriented in three dimensions, extinction, unless lower than 0.1 to 0.2, is no longer proportional to the amount of nucleic acid. (b) In general, oriented aggregates will give a lower extinction than

<sup>1</sup> This review covers the period from September, 1947 to July, 1949.

the same number of unoriented nucleic acid molecules. For complete orientation, maximum extinction will be 0.3, corresponding to 50 per cent transmission. This situation may be reversed, however, with low amounts of nucleic acid. Furthermore, structural considerations other than orientation are to be recognized, e.g., polymerization or simple aggregation. Danielli (7) emphasized the necessity of determining the effects on absorption spectra of nucleic acids in combination with cell constituents, particularly proteins.

Commoner thought that nucleic acids in living cytoplasm are essentially disoriented but that orientation and hence lower extinction values result on death of the cell. It is difficult to see, at present, how killing the cells might lead to such an orientation. Since cytolytic phenomena frequently proceed to the point where submicroscopic particulates are disintegrated (see Fractionation), there is a good chance that reaggregation, or combination with new cell constituents, may be of greater significance than orientation.

*Consistency.*—Folger (8) reported that *Amoeba proteus* responded to sudden illumination by cessation of movement. It was proposed that light may increase the elastic strength of the plasma-gel, especially at the tips of advancing pseudopodia, with consequent arrest of locomotion.

Rieser (9) determined the "viscosity" of muscle by measuring the rate of rise of oil drops injected into the protoplasm of fibers. Viscosity values ranging from 14 to 280 centipoises, with an average of 29, were obtained.

Consistency changes in the germinal vesicles of *Asterias* oocytes at several temperatures were determined by Harding (10). Thixotropic changes disappeared at temperatures above 25°C. and coagulation set in at 35°C. Protoplasmic viscosity changes during mitosis of *Chaetopterus* eggs were described by Heilbrunn & Wilson (11). There is always a question as to the significance of viscosity in protoplasmic systems. Also it would seem that localized changes in consistency, e.g., formation of spindles, asters, or cortex, may be more important than overall changes in protoplasmic consistency.

Seifriz & Pollack (12) proposed that stimulation by xanthine or opiates solates protoplasm while depression by anesthetics causes gelation. Increased activity can be correlated with dispersal or relaxing of the protein units while suppressed activity

results from aggregation or tightening of interlocking linear units (see Fibrillization).

**Zeta potentials.**—Kölbel (13) compared the isoelectric points (IEP) of living and dead yeast cell protoplasm. Living cells gave IEP values of pH 6.2 to 6.4, and dead cells, pH 4.8 to 4.9. Nolte (14) reported an IEP for ergastoplasm of pancreatic cells, following alcoholic fixation, of pH 3 to 3.4. After treatment with ribonuclease the IEP not only changed to pH 5 to 6, but the birefringence of ergastoplasm disappeared, indicating that ribonuclease must have removed the components primarily responsible for birefringence, i.e., the oriented ribonucleates. Apparently, several free acidic groups (phosphoric?) must exist in ergastoplasm to account for its low IEP. Studies on variation of IEP with age in plant cells were reported by Konarev (15).

Surface zeta potentials of *Pseudocentrotus* eggs were measured by Dan (16). Zeta potentials of *Strongylocentrotus* eggs in media containing calcium were less negative than in the absence of calcium. Still more striking were the effects of cerium ions. Dan (17) found that the addition of cerium chloride to sodium chloride solutions not only made the zeta potentials less negative but as the concentration of cerium was increased, the sign of charge was actually reversed. For example, in 0.5 M NaCl+0.1 M CeCl<sub>3</sub>, the zeta potential was +32.3 mv., while in 0.5 M NaCl, the zeta potential was -39.7 mv. These changes in zeta potential signify that calcium and cerium ions become adsorbed at the cell surface.

**Structural.**—Chambers (18) injected oil drops into the axoplasm of giant nerves of the squid and found that the drops assumed ovoid shapes along the long axis of the nerve. After agitating the axoplasm with a microneedle near the oil, the drop assumed a spherical shape. On subcooling (-3°C.), and inducing freezing of the axoplasm, icicles were formed in the shape of cylindrical rods parallel to one another and to the long axis of the nerve. Chambers concluded that the axoplasm consists of ultra-microscopically arranged material, presumably in a gel state, which reverts to a sol on injury [see also Powell (19) and Olivecrona *et al.* (20)].

Chambers further stated that the pH changes after agitating the nerve axoplasm were identical to those produced in the protoplasm of other living cells. Yolk of the *Fundulus* egg, on the other hand, exhibited no pH changes when similarly treated.

## SPECIAL REACTIVITIES OF CELLULAR COMPONENTS

Ely & Ross (21) failed in their attempts to remove nucleates from the nuclei of living fowl erythrocytes with desoxyribonuclease depolymerase. It was suggested that the depolymerase was inactive on living nuclei because either the cell membranes are impermeable or the nucleates in living cells are refractory to the enzyme. The latter is indeed possible in view of the anomalous absorption of ultraviolet light by nucleic acid-containing cell structures.

Duryee (22) observed that high doses of x-rays caused immediate fragmentation of egg chromosomes, loss of lateral chromomere loops, and vacuolization of nucleoli only when the nuclei were surrounded by cytoplasm (*Triturus* eggs). X-ray damage to nuclear components is not primarily a direct effect, but as Duryee proposes an indirect one, probably a result of chemical changes in the cytoplasm induced by radiation.

Nonhistone proteins can be removed in large amounts by extraction of the nuclei with physiological saline solutions. Accordingly, photometric measurements of nuclei in fixed tissues showed a higher proportion of protein than has been reported from isolated nuclei or chromosomes [Pollister & Leuchtenberger (23), Pollister & Ris (24)].

The development of new basophilic inclusions in the cytoplasm of myeloma cells treated with stilbamidine was reported by Snapper & Schneid (25). Snapper *et al.* (26) later found that these basophilic bodies contained ribonuclease and stilbamidine. The formation of stilbamidine-nucleates in the cytoplasm of susceptible cells was predicted by Kopac (27) on the basis of surface chemical action of stilbamidine on nucleoproteins. Basophilic inclusions, with a possible etiological significance, were seen by Grand & Chambers (28) in the cytoplasm of cells obtained from Hodgkin's disease tissues.

Wildman & Bonner (29) separated the cytoplasmic proteins, extracted from spinach leaves, into two fractions. One fraction, representing 70 to 80 per cent of the cytoplasmic proteins, at pH 6.4, was nearly homogeneous electrophoretically. The second fraction, obviously a mixture of several proteins, was not electrophoretically homogeneous.

Engström & Jakus (30) devised a method for determining intracellular proteins by x-ray microspectrography. Engström

& Lindström (31) recently described a method also involving x-ray techniques for determining the masses of cell structures. Evidence was reviewed by Aleksandrov (32) for the theory that responses of cells to external stimuli are due to the denaturation of cytoplasmic proteins [however, see Fractionation].

#### PERMEABILITY

The active participation of protoplasm in permeability is being recognized. At long last, there are indications that the shackles hitherto held securely by the plasma membrane concept have become unloosened.

*Ion exchange and phosphate turnover.*—Alkaline phosphatase activity of cell nuclei closely parallels the rate of phosphate exchange as well as desoxyribonucleic acid turnover [Brachet & Jeener (33, 34)]. Nickerson *et al.* (35) have evidence to indicate a close relationship between nucleic acids and alkaline phosphatases in yeast cells. Brooks & Chambers (36) found that  $P^{32}$  penetrated unfertilized *Strongylocentrotus* eggs at slow and constant rates, however, fertilized eggs rapidly accumulated  $P^{32}$ . Lindberg (37) described essentially the same effects with *Psammechinus* eggs and concluded that the accumulation of  $P^{32}$  is coupled with adenosinetriphosphate (ATP) turnover. Related to these investigations is the work of Connors & Scheer (38), who reported that *Strongylocentrotus* eggs not only contain adenosinetriphosphatase but there are indications that adenosinetriphosphatase activity increases on fertilization. An enzyme capable of hydrolyzing ATP was localized in the cell surfaces of living yeast cells [Rothstein & Meier (39)]. It would be highly desirable to know if adenosinetriphosphatase or apyrases are localized in the cell surfaces or in the cortex of marine eggs.

The rapid uptake of  $P^{32}$  by fertilized *Arbacia* eggs was strikingly diminished by 4,6-dinitro-*o*-cresol [Abelson (40)]. Since most of the  $P^{32}$  was subsequently localized in the trichloroacetic acid soluble fraction, it is possible that ATP synthesis may have been partially blocked by dinitro-*o*-cresol.

Chambers *et al.* (41) on centrifuging fertilized *Lytechinus* eggs containing  $P^{32}$  into light and heavy fragments found twice as much  $P^{32}$  in the light fragments as in heavy fragments. These data show that the fragment which contains mainly the cytoplasmic matrix has a higher  $P^{32}$  turnover than the fragment consisting essentially of yolk and other granules.

Abelson & Duryee (42) found that approximately 10 per cent of the sodium in ovarian eggs of *Rana pipiens* exchanges with  $\text{Na}^{24}$  while potassium exchanges with  $\text{K}^{42}$  slowly. On thermal death, all sodium becomes exchangeable and the previously accumulated potassium escapes. By radioautographic technique, Duryee & Abelson (43) showed that the accumulation of  $\text{Na}^{24}$  is higher in the nucleus than in the cytoplasm, indicating more exchangeable sodium in nuclei.

About 15 per cent of the potassium was exchangeable with  $\text{K}^{42}$  in unfertilized *Strongylocentrotus* and *Arbacia* eggs. On fertilization, the exchangeable fraction reached 85 to 90 per cent of the total potassium. Moreover, the rates of exchange were strikingly reduced by low temperatures or by sodium cyanide. For example, the  $Q_{10}$  for potassium exchange was 2.0, while concentrations of sodium cyanide ranging from 0.0001 to 0.001 *M* reduced potassium exchange by a factor of 2 or 3 [Chambers *et al.* (44)]. A clear relationship between potassium exchange and cell metabolism seems to be established by these results.

Rothenberg & Feld (45) reported that the concentration of  $\text{K}^{42}$  in the axoplasm of giant nerve fibers of the squid increased to twice the external concentration within an hour. Although the initial penetration of  $\text{Na}^{24}$  was rapid for the first 15 to 20 min., the final concentration was only approximately 25 to 30 per cent of the external concentration. The apparent rates of penetration and equilibria for each ion were consistent with the amounts initially present in the axoplasm, i.e., potassium > sodium > calcium.

Permeability constants for sodium and potassium ions in muscle cells, according to Harris & Burn (46), are 0.0004 and 0.0038 cm. per hr., respectively. Levi & Ussing (47) found that the half replacement of  $\text{Na}^{23}$  by  $\text{Na}^{24}$  in isolated sartorii fibers required about 30 min. Increasing the potassium concentration of the external medium did not appreciably modify exchange rates of  $\text{Na}^{24}$  for  $\text{Na}^{23}$ . The transport of ions across various membranes was reviewed by Ussing (48, 49).

Cells responsible for the secretion of chloride in *Fundulus* gills are packed with mitochondria oriented in the long axis of the cell. An excretory vesicle is almost invariably present near the free surface of the cells in sea water-adapted fishes [Copeland (50)]. Recently, Pettengill & Copeland (51) demonstrated that alkaline phosphatase activity is localized in the cytoplasm which surrounds the excretory vesicles of chloride secreting cells. Phos-

phatase activity was strikingly increased on transferring the euryhaline fishes from sea water to fresh water. One is strongly tempted, as Pettengill & Copeland have done, to consider chloride secreting cells as a system in which osmotic work, an energy consuming reaction, is cytologically coupled with an energy donating mechanism, i.e., the phosphatases.

*Nonelectrolytes.*—Studies on the effects of cyanide, fluoride, arsenious oxide, and iodoacetate on beef and fowl erythrocytes are believed to indicate that permeability to nonelectrolytes is independent of the energy derived from either aerobic or anaerobic metabolism [Hunter (52)]. The permeability of fowl erythrocytes to glycerol likewise does not depend on energy derived from cell metabolism [Hunter (53)]. On the other hand, Lefevre (54) showed that the permeability of human erythrocytes to glycerol was depressed by  $\text{Cu}^{++}$ ,  $\text{Hg}^{++}$ , iodine, *p*-chloromercuribenzoate, and phlorhizin. The permeability to glucose was depressed by iodine and phlorhizin, more so by  $\text{Hg}^{++}$  and *p*-chloromercuribenzoate, but not by  $\text{Cu}^{++}$ . Le Fevre suggested, with justification, that the intermediation of sulfhydryl groups at the cell surface, probably by enzymatic phosphorylation, is an essential step in the transfer of glycerol, glucose, and similar substances across human red cell membranes.

*Water.*—The osmotically inactive fraction increased from approximately 0.08 in unfertilized *Arbacia* eggs to approximately 0.28 in fertilized eggs [Shapiro (55)]. Since the fertilized eggs were measured in hypotonic sea water, there is a question whether the hyaline layer contributed to the osmotically inactive fraction, e.g., by preventing the eggs from attaining their maximum potential equilibrium volume. Equilibrium volumes of fertilized eggs should therefore be determined in calcium free media in order to eliminate the hyaline layer. In view also of the striking increase in exchangeable potassium on fertilization (44), it is impossible to assign the protoplasmic significance of the inactive fraction. In fact, one may go further and question the source of the osmotically active fraction!

Mitochondria and other inclusions, all designated by the term cytochondria, constitute an osmotic system within the cytoplasm of liver and kidney cells [Opie (56)]. Exposure of liver cells to hypotonic solutions for short periods produced swollen cytochondria and, on return to isotonic media, the cytochondria shrank to nearly normal size. Cytoplasmic basophilia was reduced on

exposing the cells to water, but this effect could be significantly prevented by isotonic solutions of sodium or potassium chloride, and even further delayed by hypertonic media. The loss of basophilic substances, presumably nucleic acids, suggests that cytochondria on swelling also suffer some disintegration—at least enough to release the basophilic substances previously organized into the structures of cytochondria. The effects of these changes in intracellular structures on osmotic equilibria are difficult to evaluate.

Thermodynamic aspects of active (nonosmotic) water absorption were discussed by Levitt (57). Kitching (58) has continued his studies on the osmoregulatory capacity and functions of contractile vacuoles.

#### NUCLEO CYTOPLASMIC INTERRELATIONS

Although important cooperation between cytoplasm and the nucleus has been inferred, a clear-cut role of the nucleus except during karyokinesis has been lacking. Several studies during the past two years establish important interrelationships of nucleus with cytoplasm.

Weiss & Hiscoe (59) and Weiss (60) concluded that growth during nerve regeneration, e.g., the production of new protoplasm, occurs solely at the base of the nerve fiber in the nucleated part of the cell. The new axoplasm is then pushed distally to compensate for the injured region. It would seem then that in nerve fibers, at least, proteins cannot be synthesized in the peripheral cytoplasm.

Barr & Bertram (61) have shown that nucleolar satellites, in cat neurons, during intense synthesis of ribonucleates move from the nucleolus towards the nuclear membrane. In some instances, the satellites were found lying in contact with the nuclear membranes. Other related papers are those of Brachet (62) and Sparrow & Hammond (63).

Marshak (64) found that  $P^{32}$ , during the first 3 hr., was held in the same nucleoprotein fraction of both mitotic and nonmitotic nuclei of rat liver cells. Subsequently, in the mitotic cells,  $P^{32}$  was localized in desoxyribonucleic acids, while in nonmitotic cells, the  $P^{32}$  passed into the ribonucleic acids. This nucleoprotein may therefore be considered as a precursor of both types of nucleic acids.

Chambers (65) proposed the name karyocytoplasm for the mixture of nucleoplasm and cytoplasm formed during maturation

of Echinoderm and other invertebrate oocytes. Asters cannot develop until the karyocytoplasm has ripened, a process which normally reaches completion a few minutes before formation of the first polar body. The egg nucleus delays the formation of the sperm aster in *Asterias* eggs, while the male pronuclei accelerate the maturation of the oocytes [Chambers & Chambers (66)].

The cortex of sea urchin eggs undergoes a progressive orientation and condensation of intermicellar space during maturation. In *Paracentrotus* oocytes, following microincineration, the ashes are uniformly distributed while in mature eggs, there is a distinct accumulation of ashes (possibly calcium) in the cortex. Cortical birefringence seems to be an expression of submicroscopic structure which is related to ripeness and fertilizability of the egg [Monroy (67)]. Thus, cortical gelation as well as aster formation requires ripened karyocytoplasm.

The hyaline zone obtained in mature starfish eggs, by centrifugation, differs strikingly in surface chemical properties from the hyaline nucleoplasm of the germinal vesicle [Kopac (68)]. Spontaneous Devaux effects quickly appeared on oil drops injected into the granular zones of centrifuged eggs, but not in the hyaline zones. In centrifuged oocytes, Devaux effects were produced at the same time in both the granular zones and in hyaline nucleoplasm. Apparently, the substances released on breakdown of the germinal vesicle become dispersed in the cytoplasm in a way that facilitates their centrifugal displacement. Either the nucleoplasm is adsorbed on and carried by the denser cytoplasmic granules or else the substance itself is particulate and with a high density.

The most spectacular cytoplasmic inclusions appear during mitosis of animal cells in the forms of spindles and asters. The mechanics of metaphase formation were reviewed by Schrader (69) and Bonnevie (70). Rybak (71) proposed that the formation of cortex or asters either involves an interaction between protamine or histone and certain cell constituents or depends on the high viscosity of nucleoproteins. The interpretation involving nucleoproteins is partly supported by Brachet & Jeener (72), who pointed out that the structural proteins in cells are mixtures of cytoplasmic and nuclear components (Chambers' karyocytoplasm?) with their special physical properties arising from desoxy-ribonucleohistones. Gelation phenomena associated with spindle and aster formation can be prevented by heparin preparations [Heilbrunn & Wilson (73)]. Since heparin is basophilic, it could

compete with structural basophilic substances of the cell and thereby interfere with astral gelation.

Ribonucleate granules exist between the astral rays of *Ascaris* eggs at the metaphase, and at anaphase these granules migrate towards the polar positions to form basophilic caps at opposite ends of the spindle [Pasteels (74)]. The mitochondria of mouse pancreatic cells, during all phases of mitosis, always move to become symmetrically arranged in relation to the plane of cleavage, an arrangement which reminds one of the behavior of chromosomes during mitosis [Christiansen (75)].

Centrosomes, according to Hughes & Swann (76), are interpreted as centers of orienting forces which form the "contractile mechanism of the spindle from isotropic protoplasm." Polarization optics revealed that the orientation of spindle substance in chick embryonic cells, in tissue culture, was higher at the poles, near the centrosomes, and weaker at the equator. It was concluded that anaphase movement is due to a contractile mechanism operating from the spindle poles [see also Ris (77)].

Anaphase separation in *Chaos chaos*, on the other hand, consists in pushing the daughter chromosomes apart by elongation of the interzonal spindle. When the daughter chromosomes are impeded in their movements, the chromosomal fibers crumple and the intersonal fibers become buckled [Berkeley (78)].

#### FRACTIONATION OF SUBCELLULAR PARTICULATES

Recent investigations on the fractionation and isolation of cytoplasmic inclusions from cell homogenates present the following problems: (a) changes in particulates induced by disintegration of the cell and by homogenizing media, (b) intracytoplasmic physiological media, (c) methods of fractionation, and (d) physical and biochemical properties of the isolated particulates. Literature on these topics is extensive and space is available for considering only the key papers.

*Effects of cytolysis.*—In many instances, drastic changes occur in the structures of cytoplasmic inclusions on disintegration of the cell. These changes include, *inter alia*, partial or complete disintegration, change of basophilic to acidophilic properties, agglutination of granules, increased susceptibility of cytoplasmic proteins to surface denaturation, and so on. Robbie (79) pointed out that cellular structures require energy for their maintenance. For example, the respiratory energy release in *Echinarachnius* eggs

is not only blocked by hydrogen cyanide, but structural breakdown also occurs. In *Arbacia* eggs, on the other hand, sufficient energy to maintain structure may be acquired by glycolytic mechanisms.

If an *Asterias* oocyte is cytolyzed within 60 sec. after injection of an oil drop into the cytoplasm, the surface denaturation of the proteins released by cytolysis is so extensive that the entire interfacial area becomes occupied by protein molecules in various stages of unfolding. The unfolding of these molecules causes the interfacial area to expand thereby producing a crinkled interface—the Devaux effect [(68)].

Other papers dealing with cytolytic phenomena are those of Zollinger (80), Dufrénoy (81), Maculla & Cowles (82), Dustin (83), Pigofí (84), Monné (85), Höfler (86), Williams & Frantz (87), and Holtfreter (88).

*Intracytoplasmic physiological media.*—Various media, including distilled water, salt mixtures, buffers, citric acid, etc., have been used for fractionating and isolating subcellular particulates. One of these, used by Hogeboom *et al.* (89), contains sucrose at high concentrations.

There is a serious question as to the desirability of using any of these media [Chambers (90)]. New intracytoplasmic physiological media should be developed and evaluated by methods involving microinjection and microsurface chemistry. Experimental media that, on microinjection, produce no appreciable disturbances in the cytoplasm, nor changes in structure and properties of mitochondria, microsomes, and nuclei, streaming, or sol-gel phenomena, might be expected to preserve formed components, after disintegration of the cells, in reasonably native states for subsequent fractionation. There is still no assurance that these isolated inclusions will be in their native condition. The probability of their being native, however, should be greater under these conditions than if the media produced drastic alterations of cellular structures on microinjection.

The main clues to the development of ionic intracellular media are that, in general, potassium ions predominate over sodium ions in cytoplasm and that calcium ions are frequently bound or their free concentration is extraordinarily low. In addition, the pH of the medium should approximate protoplasmic pH (6.6 to 7.0), and the medium should also match the apparent osmotic activity of the cytoplasm.

The optimum intracellular medium for ameba cytoplasm as

developed by Kassel (91) contained  $0.042\text{ }M\text{ KCl} + 0.017\text{ }M\text{ NaCl} + 0.0015\text{ }M\text{ CaCl}_2 + 0.001\text{ }M\text{ MnCl}_2$ . This medium, modified to contain  $0.0004\text{ }M\text{ CaCl}_2$  and no  $\text{MnCl}_2$ , has been used by Kallman (92) for the isolation of particulate fractions, rich in alkaline phosphatase activity, from the intestinal mucosa.

Measurements of the surface chemical properties of cytoplasm, however, clearly indicated that media otherwise satisfactory for ameba cytoplasm, significantly increased the denaturation of the cytoplasmic proteins at oil/water interfaces. Previous work has shown that cytoplasmic proteins in intact cytoplasm do not become surface denatured at experimentally introduced oil/water interfaces [(68)]. The ideal aqueous medium should allow no more surface denaturation than that produced by the injection of an inert oil drop. Obviously, a good intracytoplasmic physiological medium will need other factors besides electrolytes. Among the various factors to be considered are protectors against protein denaturation, inhibitors of phosphatases, apyrases, cathepsins, and so on.

*Methods of fractionation.*—Most methods now used for separating the various particulate fractions are based on differential centrifugation [(89)]. By this method, American investigators have obtained four principal fractions, i.e., nuclei, large granules including mitochondria and similar granules, submicroscopic particulates, and supernatant residues. Determinations of sedimentation constants of the various particulates with the analytical ultracentrifuge and application of such data should be a fruitful approach to the problem of recovering homogeneous fractions.

An extremely promising method, developed by Riley (93), is based on chromatography. The agent of Chicken Tumor I (Rous Sarcoma virus) (93) as well as enzymatically active pigment granules [Riley *et al.* (94)] have been successfully concentrated from cell homogenates. Chromatography may permit a separation of particulates on the basis of physicochemical properties which hitherto has been impossible by differential centrifugation since this method distinguishes only between mass, density, or, in some instances, shape.

Villela (95) reported on the isolation of snake erythrocyte nuclei. Vendrely & Vendrely (96) isolated spermatocyte nuclei; while Mirsky & Ris (97) isolated chromosomes. The use of ultrasonic radiation for disintegrating cells was described by Prudhomme & Grabar (98).

*Physical and biochemical properties.*—Hogeboom *et al.* (89) stated that opalescent suspensions of submicroscopic particles obtained from liver cells exhibited birefringence of flow. Whether these asymmetrical particles represent the fibrillar structure of protoplasm (see Fibrillization) believed to be responsible for sol-gel phenomena is a question, owing to the unphysiological nature of the medium. For example, Kassel (91) showed that the injection of 0.88 *M* sucrose into the ameba produced a localized coagulation and extensive agglutination of the microscopically visible particles as well as anomalous sol-gel reactions.

The following representative papers deal primarily with the enzymatic activities of mitochondria and submicroscopic particulates. Schneider *et al.* (99), Kennedy & Lehninger (100), Hogeboom (101), Schneider (102), Price *et al.* (103), du Buy *et al.* (104), and Dalton *et al.* (105). Papers dealing with chromosomes are: Mirsky & Ris (106), and Stern (107). Papers that deal with protoplasmic basophilia and presumably with the submicroscopic particulates are: Beams (108), Brachet (109), Lehmann (110), Brenner (111), Nolte (14), Davidson *et al.* (112), Jeener (113), and Kopac (114).

#### SUBMICROSCOPIC STRUCTURES

Considerable strides have been made in demonstrating cell structures with phase contrast microscopy and submicroscopic structures with the electron microscope. Electron micrography is worthy of review even though the reality of certain structures seen in the photographs may be questioned.

The electron micrographs of normal rat cells, in tissue culture, described by Porter & Thompson (115), showed large numbers of small granules, approximately 100  $m\mu$  in diameter in the endoplasm. In rat sarcoma cells, these granules are more abundant, frequently paired or dumb-bell shaped, and may even form beaded strands. These granules are similar in size and shape to those obtained in the submicroscopic particulate fractions of homogenized cells [see also Claude *et al.* (116)]. Epithelial tumor cells from mammary gland carcinomata also show cytoplasmic granules frequently lined up to form beaded strands of endoplasmic reticulum [Porter & Thompson (117)]. Bang & Gey (118) described a fibrillar structure in an otherwise homogeneous ectoplasm of rat fibroblasts. The fibrils, 10 to 100  $m\mu$  wide, converged and diverged in fan-like formations or else they gathered together in long

bands of varying widths, sufficiently thick to be seen with phase contrast. Granular microsomes were also evident.

The protoplasm of spread and shadow-cast thrombocytes is composed of a network of small fibers spreading in two directions, some radiating and others circular [Bessis & Bricka (119)]. These fibers are apparently composed of spheres 25 to 75  $m\mu$  wide, joined by small bridges of material. Such fibers are similar to the endoplasmic reticulum described by Porter & Thompson (117).

The recent paper by Hillier *et al.* (120) revealed considerable submicroscopic structure in bacteria. The fine structure of bacterial protoplasm was interpreted as a delicate three dimensional lattice in which the trabeculae consist of aggregates of the order of protein molecules.

Wyckoff (121, 122) described the development of new bacteriophage particles in the protoplasm of infected and lysed bacterial cells. Bacterial protoplasm was converted into phage within 15 min. The clumps and chains of small particulates suggested the same kind of reproduction often seen in bacterial growth. The particles may therefore multiply by division at the expense of bacterial protoplasm.

Numerous pairs along with occasional chains and small clumps of equine encephalomyelitis virus particles were frequently seen in electron micrographs of infected tissue culture cells [Bang & Gey (123)]. Several stages showing division of pairs suggested that the multiplication of virus particles proceeds by simple binary fission.

Electron micrographs of disintegrated calf thymus lymphocytes showed networks of fibrils 20 to 70  $m\mu$  wide. Fibers, previously treated with lanthanum acetate, could be resolved into striated ultrafibrils, 8 to 10  $m\mu$  wide. X-ray diffraction and ultracentrifugal data suggested that these fibrils consist of single desoxyribonucleoprotein molecules arranged in a spiral [Calvet *et al.* (124)].

Pease & Baker (125) believe that certain particulates seen in electron micrographs of thin sections of *Drosophila* salivary gland chromosomes may represent the gene. Feulgen positive and ultraviolet absorbing regions of salivary gland chromosomes are also the regions of maximum density to electronic beams [Schulz & MacDuffee (126)].

Electron micrographs indicate that the nuclear membrane of

amphibian oocytes is a compound structure. One component is a porous sheet composed of pores approximately 30  $\mu$  wide arranged periodically in a hexagonal array. The other component, a membrane with no evident fine structure, closely over- or underlies the porous structure. The structureless membrane may control the permeability properties of the nuclear membrane while the porous structure probably serves as a mechanical support [Callan *et al.* (127)].

#### MECHANISMS AND SIGNIFICANCE OF FIBRILLIZATION

Intracellular fibrillization comprises one of the major problems in cell physiology. It is generally agreed that gelation requires the formation of three dimensional networks from fibrillar units [Ferry (128), also see electron micrographs of fibrin clots by Hawn & Porter (129)]. The rapidity with which protoplasm undergoes sol-gel transformations must depend on the rates of forming or breaking of three dimensional networks. The problems, therefore, are to understand how fibrillae and networks may be formed rapidly and also how fibrillae may be converted into symmetrical structures, an obvious requirement for the solated condition frequently seen in protoplasm.

An example of fibrillization is the transition of globular-actin into fibrous-actin as proposed by Szent-Györgyi (130). The mechanisms involved in converting globular-actin into fibrous-actin are not, as yet, established. Another example is shown by Waugh's studies (131) on insulin fibrils. End-to-end adlineations of virus particles and of fragments from tobacco mosaic virus particles obtained by ultrasonic radiation have been described by Oster (132).

Szent-Györgyi and Waugh as well as Schmitt (133) have contributed much to our recent knowledge of protein fibrils. Their work shows that reversible fibrillar configurations can be formed from globular proteins, and not necessarily from polypeptide bundles as postulated by Monné (134) or Frey-Wyssling (135). Monné (136) recently considered that living fibrils may be regarded as monolayers of parallel oriented polypeptide chains rolled up like a scroll of paper, a pattern based on the work of Mazia *et al.* (137). It is, however, difficult to see how such fibrils could undergo defibrillization. Furthermore, Mazia's fibrils, being derived from surface denatured proteins, should be reasonably

stable and should therefore be found in cell homogenates. Nothing like this has, as yet, been recovered or identified in cell homogenates.

A cytoplasmic matrix composed of submicroscopic spherical particles or aggregates would have the consistency of a sol. In some of these spherical aggregates, the structural units, e.g., globular proteins and nucleoproteins, may already be joined end-to-end to form a prefibril. Fibrillization of such a system would merely require the unravelling and linear extension of the prefibril. Defibrillization would be the reversal of this process, or else the end-to-end bonding might collapse to yield isolated proteins and nucleoproteins originally contained within the spherical aggregate or by the fibril derived from it. This is the usual form in which one obtains proteins from cells, and also these are the proteins most susceptible to surface denaturation [(68)]. Fibrillization of the spherical aggregates would certainly increase protoplasmic consistency. A gel would develop on immobilization of the fibrils through the formation of a network, perhaps by additional bonding between units comprising the fibril.

The physiological, end-to-end bonding of the globular units may utilize ATP. For example, Munch-Petersen (138) showed that ATP expands monolayers of myosin. ATP may alter the kinetics of spreading, perhaps by facilitating the unfolding of the protein which must precede spreading [see also Cheesman & Hultin (139)]. Thus, if enough of a protein molecule were unfolded, say by action of ATP or other substances, to permit subsequent end-to-end bonding with other similar units, e.g., by van der Waals' forces interacting between the exposed nonpolar amino acid residues, a prefibril would be formed. An important point is that the intrinsic architecture of the proteins composing such fibrils is not appreciably, or irreversibly, altered.

Gelation in cell structures is an endothermic process [Marsland (140)]. Energy may be required at several places, e.g., formation of the prefibril, unfolding of prefibril to form the fibril, and bonding between fibrils to form networks. One might expect that a spherical aggregate without bonding between its units would offer more randomness, hence greater entropy, than if its units were bonded to form a prefibril. The fibrillar configuration would be still less random while networks would have the least randomness, hence lowest entropy. The entropy of chain configurations was discussed

by Ingersoll & Johnson (141) and Hermans (142). The possible relationship, as well as necessity, of energy-coupling systems to fibrillization and gelation presents an intriguing problem.

Spherical submicroscopic particles, or aggregates, may also arrange themselves in linear, bead-like configurations as shown by electron micrographs [(117)]. In all probability, these beaded strands are not the fibrils concerned directly with sol-gel phenomena. They may, however, represent the framework of a gel. For instance, if the spherical particles within such strands fibrillized, as described above, an incipient network could be easily formed.

Many fundamental problems concerned with protoplasmic growth, karyokinesis, and cytokinesis, are intimately tied in with energy-coupled reactions, intracellular fibrillization, and gelation. The increased application of the electron microscope, surface chemistry, and enzymatic cytochemistry to cells, as well as to fractions of subcellular particulates obtained under physiological conditions, should increase our knowledge of these fundamental protoplasmic phenomena. Indeed, it seems possible that cell physiology may soon undergo a fruitful renaissance.

#### LITERATURE CITED

1. BRUMBERG, E. M., AND LARINOW, L. T., *Nature*, **158**, 663 (1946)
2. RIS, H., AND MIRSKY, A. E., *J. Gen. Physiol.*, **32**, 489 (1949)
3. ELY, J. O., AND ROSS, M. H., *Nature*, **163**, 906 (1949)
4. LUDFORD, R. J., SMILES, J., AND WELCH, F. V., *J. Roy. Microscop. Soc.*, **68**, 1 (1948)
5. COMMONER, B., *Science*, **110**, 31 (1949)
6. COMMONER, B., AND LIPKIN, D., *Science*, **110**, 41 (1949)
7. DANIELLI, J. F., *Symposia Soc. Exptl. Biol., Nucleic Acid.*, **1**, 101 (1947)
8. FOLGER, H. T., *Biol. Bull.*, **93**, 45 (1947)
9. RIESER, P., *Protoplasma* (In press)
10. HARDING, D., *Proc. Soc. Exptl. Biol. Med.*, **70**, 705 (1949)
11. HEILBRUNN, L. V., AND WILSON, W. L., *Biol. Bull.*, **95**, 57 (1948)
12. SEIFRIZ, W., AND POLLACK, H. L., *J. Colloid Sci.*, **4**, 19 (1949)
13. KÖLBEL, H., *Z. Naturforsch.*, **2b**, 382 (1947)
14. NOLTE, A., *Z. Naturforsch.*, **2b**, 295 (1947)
15. KONAREV, V. G., *Doklady Akad. Nauk S.S.S.R.*, **59**, 773 (1948)
16. DAN, K., *Biol. Bull.*, **93**, 259 (1947)
17. DAN, K., *Biol. Bull.*, **93**, 267 (1947)
18. CHAMBERS, R., *Biol. Bull.*, **93**, 191 (1947)
19. POWELL, A. K., *J. Roy. Microscop. Soc.*, **66**, 35, 53, (1946); **67**, 14 (1947)
20. OLIVECRONA, H., LÖFSTRÖM, B., AND HILLARP, N., *Acta Anat.*, **3**, 344 (1947)
21. ELY, J. O., AND ROSS, M. H., *Science*, **109**, 367 (1949)

22. DURYEE, W. R., *Biol. Bull.* **93**, 206 (1947)
23. POLLISTER, A. W., AND LEUCHTENBERGER, C., *Proc. Natl. Acad. Sci. U. S.* **35**, 66 (1949)
24. POLLISTER, A. W., AND RIS, H., *Cold Spring Harbor Symposia Quant. Biol.* **12**, 147 (1947)
25. SNAPPER, I., AND SCHNEID, B., *Ann. Internal Med.*, **27**, 541 (1947)
26. SNAPPER, I., MIRSKY, A. E., RIS, H., SCHNEID, B., AND ROSENTHAL, M., *Blood*, **2**, 311 (1947)
27. KOPAC, M. J., *Acta Union Intern. Contre Cancer*, **6**, 357 (1948)
28. GRAND, C. G., AND CHAMBERS, R., *Cancer Research*, **9**, 183 (1949)
29. WILDMAN, S. G., AND BONNER, J., *Arch. Biochem.*, **14**, 381 (1947)
30. ENGSTRÖM, A., AND JAKUS, M. A., *Nature*, **161**, 168 (1948)
31. ENGSTRÖM, A., AND LINDSTRÖM, B., *Nature*, **163**, 563 (1949)
32. ALEKSANDROV, V. Y., *Soveshchanie po Belku, Akademiya Nauk S.S.S.R.*, **95**, (5 ya Koferents. Vysokomolekulyar. Soedinenigam, 1948)
33. BRACHET, J., AND JEENER, R., *Compt. rend. soc. biol.*, **140**, 1121 (1947)
34. BRACHET, J., AND JEENER, R., *Biochim. et Biophys. Acta*, **2**, 423 (1948)
35. NICKERSON, W. J., KRUGELIS, E. J., AND ANDRÉSEN, N., *Nature*, **162**, 192 (1948)
36. BROOKS, S. C., AND CHAMBERS, E. L., *Biol. Bull.*, **95**, 263 (1948)
37. LINDBERG, O., *Arkiv Kemi, Mineral. Geol. [B]* **26**, (13), 1 (1948)
38. CONNORS, W. M., AND SCHEER, B. T., *J. Cellular Comp. Physiol.*, **30**, 271 (1947)
39. ROTHSTEIN, A., AND MEIER, R., *J. Cellular Comp. Physiol.*, **32**, 77 (1948)
40. ABELSON, P. H., *Biol. Bull.*, **93**, 203 (1947)
41. CHAMBERS, E. L., WHITELEY, A., CHAMBERS, R., AND BROOKS, S. C., *Biol. Bull.*, **95**, 263 (1948)
42. ABELSON, P. H., AND DURYEE, W. R., *Anat. Record*, **101**, 653 (1948); *Biol. Bull.*, **96**, 205 (1949)
43. DURYEE, W. R., AND ABELSON, P. H., *Biol. Bull.*, **93**, 225 (1947)
44. CHAMBERS, E. L., WHITE, W., JEUNG, N., AND BROOKS, S. C., *Biol. Bull.*, **95**, 252 (1948)
45. ROTHENBERG, M. A., AND FELD, A. E., *J. Biol. Chem.*, **172**, 345 (1948)
46. HARRIS, E. J., AND BURN, G. P., *Nature*, **162**, 929 (1948)
47. LEVI, H., AND USSING, H. H., *Acta Physiol. Scand.*, **16**, 232 (1948)
48. USSING, H. H., *Physiol. Revs.*, **29**, 127 (1949)
49. USSING, H. H., *Acta Physiol. Scand.*, **17**, 1 (1949)
50. COPELAND, D. E., *J. Morphol.*, **82**, 201 (1948)
51. PETTENGILL, O., AND COPELAND, D. E., *J. Exptl. Zool.*, **108**, 235 (1948)
52. HUNTER, F. R., *J. Cellular Comp. Physiol.*, **29**, 301 (1947)
53. HUNTER, F. R., *J. Cellular Comp. Physiol.*, **29**, 313 (1947)
54. LEFEVRE, P. G., *J. Gen. Physiol.*, **31**, 505 (1948)
55. SHAPIRO, H., *J. Gen. Physiol.*, **32**, 43 (1948)
56. OPIE, E. L., *J. Exptl. Med.*, **87**, 425 (1948)
57. LEVITT, J., *Plant Physiol.*, **22**, 514 (1947)
58. KITCHING, J. A., *Nature*, **162**, 149 (1948)
59. WEISS, P., AND HISCOE, H. B., *J. Exptl. Zool.*, **107**, 315 (1948)
60. WEISS, P., *Chemistry and Physiology of Growth*, 135 (Princeton University Press, Princeton, N. J., 1949)
61. BARR, M. L., AND BERTRAM, E. G., *Nature*, **163**, 676 (1949)

62. BRACHET, J., *Growth*, **11**, 309 (1947)
63. SPARROW, A. H., AND HAMMOND, M. R., *Am. J. Botany*, **34**, 439 (1947)
64. MARSHAK, A., *J. Cellular Comp. Physiol.*, **32**, 381 (1948)
65. CHAMBERS, R., *Ann. N. Y. Acad. Sci.* (In press)
66. CHAMBERS, R., AND CHAMBERS, E. L., *Biol. Bull.*, **96**, 270 (1949)
67. MONROY, A., *Experientia*, **4**, 353 (1948)
68. KOPAC, M. J., *Ann. N. Y. Acad. Sci.* (In press)
69. SCHRADER, R., *Chromosoma*, **3**, 22 (1947)
70. BONNEVIE, K., *J. Morphol.*, **81**, 399 (1947)
71. RYBAK, B., *Compt. rend.*, **226**, 1145 (1948)
72. BRACHET, J., AND JEENER, R., *Biochim. et Biophys. Acta*, **1**, 13 (1947)
73. HEILBRUNN, L. V., AND WILSON, W. L., *Proc. Soc. Exptl. Biol. Med.*, **70**, 179 (1949)
74. PASTEELS, J., *Experientia*, **4**, 150 (1948)
75. CHRISTIANSEN, E. G., *Nature*, **163**, 361 (1949)
76. HUGHES, A. F., AND SWANN, M. M., *J. Exptl. Biol.*, **25**, 45 (1948)
77. RIS, H., *Biol. Bull.*, **96**, 90 (1949)
78. BERKELEY, E., *Biol. Bull.*, **94**, 169 (1948)
79. ROBBIE, W. A., *J. Gen. Physiol.*, **31**, 217 (1947)
80. ZOLLINGER, H. V., *Am. J. Path.*, **24**, 545, 569, 797, 1039 (1948)
81. DUFRÉNOY, J., *Rev. can. biol.*, **6**, 211 (1947)
82. MACULLA, E. S., AND COWLES, P. B., *Science*, **107**, 376 (1948)
83. DUSTIN, P., JR., *Symposia Soc. Exptl. Biol., Nucleic Acid*, **1**, 114 (1947)
84. PIGOŃ, A., *Bull. Acad. Pol. Sci. et Lettres*, **2B**, 75 (1947)
85. MONNÉ, L., *Arkiv Zool.* [A]**39**, (7), 1 (1947)
86. HÖFLER, K., *Sitzber. Akad. Wiss. Wien, Math.-naturw. Klasse.* [I]**156**, 585 (1947)
87. WILLIAMS, W. L., AND FRANTZ, M., *Anat. Record*, **100**, 547 (1948)
88. HOLTRETER, J., *J. Morphol.*, **80**, 345 (1947)
89. HOGEBOOM, G. H., SCHNEIDER, W. C., AND PALLADE, G. E., *J. Biol. Chem.*, **172**, 619 (1948)
90. CHAMBERS, R., *Biol. Revs. Cambridge Phil. Soc.*, **24**, 246 (1949)
91. KASSEL, R., *The Effects of Protein Denaturing and Anti-denaturing Agents on Protoplasm* (Master's thesis, New York Univ., 1949)
92. KALLMAN, F., *Substrate Specificities and Inhibition of Intracellular Phosphatases* (Doctoral thesis, New York Univ., 1949)
93. RILEY, V. T., *Science*, **107**, 573 (1948)
94. RILEY, V. T., HESSELBACH, M. L., FIALA, S., WOODS, M. W., AND BURK, D., *Science*, **109**, 361 (1949)
95. VILLELA, G. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 398 (1947)
96. VENDRELY, R., AND VENDRELY, C., *Experientia*, **4**, 434 (1948)
97. MIRSKY, A. E., AND RIS, H., *J. Gen. Physiol.*, **31**, 1 (1947)
98. PRUDHOMME, R. O., AND GRABAR, P., *Ann. inst. Pasteur*, **76**, 460 (1949)
99. SCHNEIDER, W. C., CLAUDE, A., AND HOGEBOOM, G. H., *J. Biol. Chem.*, **172**, 451 (1948)
100. KENNEDY, E. P., AND LEHNINGER, A. L., *J. Biol. Chem.*, **172**, 847 (1948)
101. HOGEBOOM, G. H., *J. Biol. Chem.*, **177**, 847 (1949)
102. SCHNEIDER, W. C., *Cold Spring Harbor Symposia Quant. Biol.*, **12**, 169 (1947)
103. PRICE, J. M., MILLER, E. C., AND MILLER, J. A., *J. Biol. Chem.*, **173**, 345 (1948)

104. DU BUY, H., WOODS, M., BURK, D., AND LACKEY, M., *J. Natl. Cancer. Inst.*, **9**, 325 (1949)
105. DALTON, A. J., KAHLER, H., KELLEY, M. G., LLOYD, B. J., AND STRIEBICH, M. J., *J. Natl. Cancer. Inst.*, **9**, 439 (1949)
106. MIRSKY, A. E., AND RIS, H., *J. Gen. Physiol.*, **31**, 7 (1947); *Nature*, **163**, 667 (1949)
107. STERN, K. G., *Scientia (Milan)*, **82**, 74 (1947)
108. BEAMS, H. W., *Proc. Soc. Exptl. Biol. Med.*, **66**, 373 (1947)
109. BRACHET, J., *Experientia*, **3**, 329 (1947)
110. LEHMANN, F. E., *Rev. suisse zool.*, **54**, 246 (1947)
111. BRENNER, S., *S. African J. Med. Sci.*, **12**, 53 (1947)
112. DAVIDSON, J. N., LESLIE, I., AND WHITE, J. C., *J. Path. Bact.*, **60**, 1 (1948)
113. JEENER, R., *Biochim. et Biophys. Acta*, **2**, 633 (1948)
114. KOPAC, M. J., *Spec. Pubs. N. Y. Acad. Sci.*, **4**, 423 (1948)
115. PORTER, K. R., AND THOMPSON, H. P., *Cancer Research*, **7**, 431 (1947)
116. CLAUDE, A., PORTER, K. R., AND PICKELS, E. G., *Cancer Research*, **7**, 421 (1947)
117. PORTER, K. R., AND THOMPSON, H. P., *J. Exptl. Med.*, **88**, 15 (1948)
118. BANG, F. B., AND GEY, G. O., *Proc. Soc. Exptl. Biol. Med.*, **69**, 86 (1948)
119. BESSIS, M., AND BRICKA, M., *Biochim. et Biophys. Acta*, **2**, 339 (1948)
120. HILLIER, J., MUDD, S., AND SMITH, A. G., *J. Bact.*, **57**, 319 (1949)
121. WYCKOFF, R. W. G., *Biochim. et Biophys. Acta*, **2**, 27 (1948)
122. WYCKOFF, R. W. G., *Proc. Soc. Exptl. Biol. Med.*, **71**, 144 (1949)
123. BANG, F. B., AND GEY, G. O., *Proc. Soc. Exptl. Biol. Med.*, **71**, 78 (1949)
124. CALVET, F., SIEGEL, B. M., AND STERN, K. G., *Nature*, **162**, 305 (1948)
125. PEASE, D. C., AND BAKER, R. F., *Science*, **109**, 8 (1949)
126. SCHULZ, J., AND MACDUFFEE, R. C., *Science*, **110**, 5 (1949)
127. CALLAN, H. G., RANDALL, J. T., AND TOMLIN, S. G., *Nature*, **163**, 280 (1949)
128. FERRY, J. D., *Advances in Protein Chem.*, **4**, 1 (1948)
129. HAWN, C. van Z., AND PORTER, K. R., *J. Exptl. Med.*, **86**, 285 (1947)
130. SZENT-GYÖRGYI, A., *Nature of Life*, **91 pp.** (Academic Press Inc., N. Y., 1948)
131. WAUGH, D. F., *Anat. Record*, **101**, 656 (1948); *J. Am. Chem. Soc.*, **70**, 1850 (1948)
132. OSTER, G., *J. Gen. Physiol.*, **31**, 89 (1947)
133. SCHMITT, F. O., *Chemistry and Physiology of Growth*, 48 (Princeton Univ. Press, 1949)
134. MONNÉ, L., *Advances in Enzymol.*, **8**, 1 (1948)
135. FREY-WYSSLING, A., *Submicroscopic Morphology of Protoplasm and Its Derivatives*, 263 pp. (Elsevier Publishing Co., Ind., N. Y., 1948)
136. MONNÉ, L., *Arkiv. Zool. [A]*, **42**(4), 1 (1949)
137. MAZIA, D., HAYASHI, T., AND YUDOWITCH, K., *Cold Spring Harbor Symposia Quant. Biol.*, **12**, 122 (1947)
138. MUNCH-PETERSEN, A., *Nature*, **162**, 537 (1948)
139. CHEESMAN, D. F., AND HULTIN, T., *Arkiv Kemi, Mineral. Geol. [B]*, **24** (49), 1 (1947)
140. MARSLAND, D., *Sci. Monthly*, **67**, 193 (1948)
141. INGERSOLL, H. G., AND JOHNSON, A. A., *Nature*, **162**, 225 (1948)
142. HERMANS, J. J., *Trans. Faraday Soc.*, **43**, 91 (1947)

## RADIANT ENERGY

BY ABRAHAM EDELMANN

*Biology Department, Brookhaven National Laboratory,  
Upton, Long Island, New York*

The uses of radiation in biological research and therapy, and its potential military application, have increased the need for an understanding of radiation effect, thus heightening interest in this field. In this regard, the impetus and support of the Atomic Energy Commission's program has played a considerable part.

The period covered by this review, July 1, 1948 to June 30, 1949, has been marked by the large number of articles on the various aspects of radiation. This is due in some part to the declassification and publication of many reports from Atomic Energy Commission (AEC) laboratories, hitherto unpublished for security reasons. Many articles which were published during this period in scientific journals had appeared earlier as Manhattan District and AEC declassified documents. A number of these were reviewed in volume XI of this series and where possible were eliminated from this article. Therefore, it may appear that more omissions have been made than space limitations warrant.

The first available volume of the National Nuclear Energy Series deals with the histopathology of irradiation from external and internal sources (1). It literally and figuratively illustrates cytological and histological effects of  $\alpha$ -,  $\beta$ -,  $\gamma$ - and x-rays, and fast and slow neutrons.

Two sections of a bibliography on atomic energy are of interest. These are on the "Biological and Medical Effects of High Energy Radiation" (2) and "Isotopes in Biology and Medicine" (3). While these are not quite complete and the cataloging leaves much to be desired, they admittedly represent a start on a much needed work. The first volume of *Advances in Biological and Medical Physics* (4) contains chapters on radioactivity fundamentals, protection from and effects of atomic bomb irradiation on the Japanese, in addition to several chapters dealing with tracer applications. Published reports of two conferences, one on the use of radioiodine (5) and the other on the application of nuclear physics in biology (6) appeared, each containing articles of interest to physiologists.

Another need was filled by a set of tables of radiation effects on

mammals, including man, and insects, compiled by Dowdy (7). These include effects on gonads, incidence of leukemia, hematological effects other than leukemia, acute total body irradiation effects, embryological effects, neutron-roentgen ratios, mortality tables, longevity tables and others.

*Safeguards.*—The handling of radiation equipment and radioactive materials involves hazards and problems which are not yet fully understood. With large numbers of laboratories and hospitals using radioactive isotopes and high energy radiations, more attention should be paid to methods of protection of both the public and personnel. Popular misconceptions concerning radiation should be clarified by education. This is properly a function of the Atomic Energy Commission. Wolf (8) attempts to place some of the more worrisome hazards, such as sterilizing and genetic effects, in their proper perspective.

One of the more pressing problems at installations using radioactive materials is that of adequate waste disposal. Gorman (9) stresses the need for sanitary engineers with training in nuclear physics, while Gorman & Wolman (10) discuss the problem in greater detail from the points of view of the public health engineer and industrial hygienist respectively. Western (11) suggests the following possibilities of disposal: (a) dilution to avoid concentration by adsorption or absorption, (b) dilution with one or more stable isotopes of the same chemical element, (c) storage to allow decay to stable isotopes, (d) removal from process fluids and concentrations by ion exchange, adsorption, precipitation, sedimentation, extraction, and evaporation, and (e) placing in containers and disposal of materials in the ocean. Another aspect of this problem is that of disposal of gaseous radioactive waste which is discussed by Beers (12); factors concerned in determining the tolerance concentration of radioactive gases in air are considered by Failla (13).

Personnel protection is chiefly accomplished by the education and training of the worker handling the radioactive material (14), the difficulties arising not from their use but their misuse (15). The hazards to patients are due, for the most part, to errors by the physician in calculation of doses, according to Chamberlain *et al.* (16).

A bibliography listing articles on radiation protection has appeared (17), and discussions of these dangers and measures used

at various sites to combat them are the topics of a number of papers (14, 15, 18 to 32). Protective procedures against x-rays (33, 34, 35) and protective requirements for one million and two million volt x-ray installations (36) are given. Knowledge gained by work on other forms of radiation has led the American Medical Association to suggest that benign conditions should not be treated by x-rays due to the possible harmful sequelae, unless other forms of therapy fail (37). It has been suggested by Perry that daily doses of 100 mg. of potassium iodide be given persons exposed to radioiodine in the atmosphere, to act as a diluent to absorbed radioiodine (38). Skanse (39) concludes that so-called "tracer" doses of  $I^{131}$  may alter the normal thyroid function and Lukens (40) describes complicating sequelae following x-irradiation of the thyroid gland.

Microwave radiation, particularly at the 10 cm. wave length and even at low field intensities, injures animals and should be treated with the same respect as x-rays,  $\alpha$ -rays and neutrons, according to Salisbury, Clark and Hines (41).

Evans (42) has discovered that 1 n (neutron unit) of fast neutron irradiation is approximately equivalent to 10 r (roentgens) of x-rays. The effect of slow neutrons on tissues was found by Snider (43) to be similar to that of x-rays.

Recognizing the requirements peculiar to radiobiological laboratories, Norris (44) points out the desirability of separate rooms for (a) the preparation of active materials in a suitable form, (b) the administration and (c) care and housing of such biological specimens (d) preparation of samples for radioactive measurements and (e) measurement of radioactivity. This would minimize the danger of cross contamination. Levy describes physical facilities for laboratories handling isotopes at the microcurie and millicurie levels (45). Techniques of surveying and monitoring radiation are reviewed by Morgan (46), and discussions on measuring dosages of radiation are described by several authors (47 to 50). Recommendations for the construction and operation of laboratories for animal experimentation with radioactive materials have appeared (51).

*Measurement.*—Cassen & Curtis (52) have fitted a hypodermic needle with an internally reflecting light pipe which conducts light emitted from a small amount of a substance which fluoresces or

scintillates on exposure to  $\alpha$ -,  $\beta$ -,  $\gamma$ - or x-rays. The light is piped to a photomultiplier tube and then recorded, thus making it possible to obtain a more accurate measurement of the radiation actually reaching a deep tissue. A method of calculating the radiation received by tissue from radioactive substances distributed in the body is offered by Wahlberg (53).

The measurement of fast neutrons is technically difficult and of practical interest. Dessauer & Lennox (54) suggest the placing of a cadmium strip near an x-ray film to intensify the secondary radiation. Radioautographs are used to quantitatively measure local dosage rates in tissue by Dudley & Dobyns (55).

One of the most promising developments is that of the use of neutron induced radioactivity for quantitative determinations of small amounts of elements in tissue as described by Tobias & Dunn (56). Boyd uses the same method to detect impurities in other substances (57).

Many papers have appeared on atom bomb effects, preventive medical aspects and the sociological implications of the bomb. For completeness these are listed here (58 to 74).

*Mode of action.*—The ionization caused by the absorption of energy from the rays appears to be responsible for the observed effects. Work on inorganic and organic systems *in vitro* has greatly aided in our concept of the method by which living tissue is affected. Bonet-Maury & Lefort found that the amount of hydrogen peroxide produced as the result of x-radiation on water depends upon the concentration of dissolved oxygen, no hydrogen peroxide being detected in oxygen-free water. In oxygen saturated water, hydrogen peroxide production by x-rays diminishes as the temperature decreases, a definite discontinuity occurring at the transition from water to ice and no detectable peroxide being found at  $-116^{\circ}$ . After alpha radiation, however, the production of hydrogen peroxide seemed to be unrelated to either the oxygen content or temperature of the solution except, in the latter case, at the water to ice transition point (75). Barron *et al.* (76) present evidence that the products of water irradiation (x-rays), OH,  $O_2H$ ,  $H_2O_2$ , and O, oxidize *in vitro* the sulfhydryl radicals of phosphoglyceraldehyde dehydrogenase, adenosinetriphosphatase, and succinoxidase and thus reduce the activity of a sample of the enzyme. Glutathione was able to reactivate the enzyme when inhibition was only par-

tial. Heavier doses of radiation caused irreversible inhibition, allegedly by denaturation of the protein itself. This process is believed responsible for the inhibition occurring upon irradiation of the nonsulfhydryl enzymes trypsin, catalase and ribonuclease. Similar results were obtained with  $\alpha$ -,  $\beta$ -, and  $\gamma$ -rays (77).

The metabolism of rat spleen, liver, kidney, thymus, adrenal, testis and submaxillary glands after x-irradiation was studied by Barron (78), who found that in general the respiration of all tissues with the exception of thymus, and the oxidation of substrates requiring sulfhydryl enzymes, were diminished immediately after irradiation. Zirkle (79) assumes that biological effects are brought about by the formation of new compounds by chemical reactions resulting from ionizing radiations.

The physical configuration of the molecules of enzymes in a film determines its sensitivity to radiation according to Mazia & Blumenthal, who also show that a large number of enzyme molecules in such a film may be affected by the spread of the effects of a single ionization (80). Evidence for long lived excited polymers in irradiated water was obtained by Krenz (81). Further indications that irradiation products of water may be responsible for biological effects, were presented by Alper, in whose *in vitro* experiments bacteriophage S13 in dilute solution was inactivated by the hydrogen peroxide formed by ionizing radiations (82); similarly Proctor & Goldblith (83) showed that x-rays and cathode rays both had a greater destructive effect on solutions of niacin containing 5  $\mu\text{g. per l.}$  than on those containing 100  $\mu\text{g. per l.}$  Additional evidence for the indirect hit theory is provided by Miller who reports that the rate of oxidation of ferrous ions by x- and gamma radiation is independent of the ferrous ion concentration (84). Sodium thymus nucleate in aqueous solution, according to Taylor, *et al.*, breaks up into shorter fragments upon x-irradiation. This continues after cessation of the radiation, the duration being dependent upon the roentgenage delivered and independent of the radiation rate (85). Mathis and co-workers found that potassium hyaluronate solution becomes less viscous as a result of x-irradiation. This process also continued for some hours after the radiation ceased (86). The view advanced by Lea (172) that primary or direct-target type of action of radiation is more efficient than secondary radiation has been rejected by Pollard & Forro (87) who bombarded phage with deuter-

ons, by Dale *et al.* (88) in experiments on the inactivation of carboxypeptidase with x- and alpha radiation, and by Sommermeyer (89).

An interesting thesis has been advanced by Van der Werff (90), who feels that radiation interferes with the continuous destruction and regeneration of cells and tissues of animals by interfering with the assimilation processes. Mathematical derivations correlate the data presented.

Bonham found that at least 10,000 r of x-radiation were required to kill adult snails (*Radix japonica*), while the administration of 1,000 r to their egg masses resulted in retardation of development. The crawling activity of newly hatched young from eggs receiving 10,000 r was inhibited (91). Bonham *et al.* report that Fingerling chinook salmon (*Oncorhynchus tshawytscha* Walbaum) were affected in mortality, weight and length by thresholds of 250, 500 and 1,000 r respectively (92). Adult rainbow trout as reported by Welander *et al.* demonstrated radiation injuries after 500 r of x-irradiation or more, and growth in length and weight was retarded with doses as low as 50 r. The growth increment following 750 r was inversely proportional to the dose (93). In tadpoles, small doses of alpha rays were observed by Tansley *et al.* to cause cell degeneration and changes in mitotic counts which were comparable to similar doses of gamma rays. Larger amounts of alpha radiation, however, caused degeneration of potential dividing cells in numbers far exceeding those expected on a comparative basis with observed results with gamma rays (94).

*Effects on blood.*—Because of their prominence, the effects of radiation on the blood and blood forming elements have commanded a good deal of attention in the past. During this last year, however, it appears that relatively fewer studies have been made on this system. It was found by Murray *et al.* that three-week-old chickens showed decreased leucocyte counts following 600 r. The counts were decreased relatively more than those in mammals. Lymphatic tissue responded to 25 r, a threshold comparable to mammals (95). Following repeated subcutaneous injections of  $P^{32}$ , young chicks rapidly developed thrombocytopenia and agranulocytosis. The clotting time increase was comparable to, while the hemorrhage was less severe than, that in mammals (96). Fingerling chinook salmon also show the drop in circulating blood cells after

750 r and 1,250 r as well as a decline in the concentration of hemopoietic cells in the 750 r group (93).

In a fairly complete study in mice, Brecher *et al.* (97) report the almost complete disappearance of nucleated red cells from the bone marrow within 24 hr. after 400 r whole body radiation. Regeneration of the erythroid series began at about the seventh day, suppression of mitotic activity and diminution of myeloid marrow being marked during the intervening time. Granulocytopenia was severe for only a short period of time, whereas damage to lymphoid tissue was more pronounced and the lymphopenia of longer duration, despite early regeneration of lymphoid structures. Smith, Dooley & Thompson found that exposure of mice to simulated altitudes of 20,000 to 25,000 ft. at periods from one to six days following 400 r to 500 r had no effect on the course of diminution and recovery of platelets, erythrocytes and hemoglobin (98).

Jacobson & Simmons injected various amounts of radium chloride into mice, rats and rabbits. The latter appeared to be more sensitive than the other two species. In all species no significant hematological changes occurred after injection of 0.01 microcuries. Changes in the morphology of the nucleated cells of peripheral blood were observed following 0.1 and 0.2 microcuries per gm. of radium which are similar to those previously described following externally applied x-rays,  $\gamma$ -rays, fast neutrons or internal plutonium (99). Decreased leucocyte counts are also found in swine after x-irradiation (100).

While the blood changes in patients treated with x-rays, as described by Low-Beer & Stone (101), Nickson (102) and Price (103), are comparable to those described for animals, no blood changes were found in the radiology personnel exposed to 0.1 r to 0.25 r weekly (104).

It has been well established that one of the consequences of irradiation is a prolonged clotting time. This may be due to increased heparin, inasmuch as a normal calcium and prothrombin level existed, and the effect is reversed by antiheparin substances. It is suggested by Jacobson *et al.* that these antiheparin substances be used to pass the critical potential hemorrhage period (105). Other workers (106), however, report a hypothromboplastinemia following radiation. This may account for a relative increase in blood heparin. A case of thrombocytopenia purpura following the

administration of 202 millicuries of radioactive sodium over a five month period is reported by Jacox (107).

Attempts have been made to counteract hemorrhagic tendencies following radiation. In experiments performed by Clark, Uncapher & Jordon (108) some protection was afforded to guinea pigs by a week's pretreatment with a flavonoid preparation from lemons. The petechial hemorrhage and ecchymoses following 225 r of x-rays, were considerably less marked in those animals than in the untreated controls and the mortality was reduced by half. In dogs, as reported by Field & Rekers, rutin, hesperidin, and epimerized d-catechin reduced hemorrhagic signs following 350 r of x-irradiation, while hesperidin methyl chalcone, esculin, quercitrin, quercitrin and naringin had no effect (109). In mice, however, Cronkite *et al.* report that rutin significantly increased the mortality rate following irradiation (110). Kohn *et al.* (111) found no effect of rutin on the LD 50 (50 per cent lethal) dose, survival following sublethal exposures, coagulation time, thrombocyte count, total white cell count, or hemorrhage into lymph nodes or gastrointestinal tract following x-irradiation of rats. *In vitro* studies on rats and human blood showed that rutin had no effect on prothrombin time or coagulation time, nor did it prevent the action of heparin, while it did antagonize the antiheparin action of toluidine blue. Evidence that the semicarbazone of adenochrome will reduce cutaneous purpura in mice receiving 400 r x-ray doses for four days is presented by Hervé & Lecomte (112). Pyridoxine relieved some of the symptoms of radiation sickness, according to Shorvon (113).

Stearner (114) found that folic acid had no effect on x-ray induced anemia in rats and thus feels that x-rays have a direct effect on the bone marrow and that damage to viscera producing the antianemia principle is negligible in this respect. Folic acid did not affect the leucopenia of cats exposed to 200 r whole body irradiation (115) and it did not alter the hematology or clinical symptoms of swine after 400 r whole body radiation (116).

Lawrence, Dowdy & Valentine (117) point out a relationship between the life span and speed of utilization of the different morphological elements in the blood. Lymphocytes, whose life span is short, after 500 r decrease in numbers rapidly, the first drop being noticeable after 15 min. Granulocytes are not appreciably affected until 24 to 36 hr. Platelets start to disappear at 72 to 120 hr., and

erythrocytes between 120 and 168 hr. At doses of 200 r the platelets and erythrocytes are not affected, while following 100 r no large changes in reticulocyte counts were noted. Lymphocytes, on the other hand, are affected by as little as 25 r. These authors also point out that while hematological effects are not always demonstrable after small repeated doses, the average survival of groups of animals was affected, so that the cumulative dose is important. Rosenthal (118) has reported an opalescence of serum and plasma of x-irradiated rabbits which subsequently died and relates this to the death of the animal.

In experiments performed by De Bruyn, the majority of lymph nodes of rabbits are completely destroyed after 800 r or 600 r of whole body x-irradiation. Regeneration begins 21 or 14 days, respectively, after treatment. Following 400 r, the majority of the nodes are only partially destroyed. Fifty r was the smallest dose producing histologically detectable damage. Rats responded similarly to rabbits after 600 and 400 r, while 175 r in guinea pigs produced effects comparable to the lower doses in rats and rabbits. Inasmuch as the thirty-day LD 50 for the rabbit, rat and guinea pig is 800 r, 600 r and 175 r respectively, it is concluded that the intensity of lymph node damage is related to the absolute dosage and not to the LD 50 value of these species (119).

X-radiation was used by Downey as a tool in the study of regenerating rabbit thymocytes (120) from which he concluded that thymocytes are genuine lymphocytes. The largest lymphocytes of lymph nodes do not occur in the thymus, the smaller ones with pachychromatic nuclei and scanty cytoplasm being more numerous. Some lymphoblasts similar to myeloblasts occur in this organ. Schrek (121) found that the spontaneous and x-ray induced degeneration of lymphocytes in irradiated rabbit and rat thymi is associated with the formation of extranuclear vacuoles, pyknosis and fragmentation. Intranuclear acidophilic vacuoles have also been observed in thymic cells 3 hr. after irradiation with 1,000 r of x-rays. Two hours later histological examination revealed many pyknotic and fragmented nuclei. X-rays have also been used to destroy lymphocytes in studies on antibody formation and response (122, 123).

*Effects on other tissues.*—Areas comprising the testes, adrenals, and part of the kidneys of male chicks (four to six weeks old) were

x-rayed with doses varying from 1,200 to 8,400 r by Sturkie *et al.* (124). Those receiving 1,600 r were fertile when mated to females at maturity, most of those receiving 2,100 to 2,800 r were sterile, while all those receiving 5,600 and 8,400 r were sterile. There was no effect on comb growth and mating behavior. The testes were reduced in size. Warren & Dixon (125) found that the testes and ovaries of chick embryos and young chicks continuously irradiated by means of injections of  $P^{32}$  were the most radiosensitive structures and the least able to recover from injury. The primitive sex cells were the most sensitive, the spermatogenic cells were sensitive all throughout development while the ova became more radioreistant as they matured.

Male mice (LAF strain) exposed to 4.4 r or 8.8 r of gamma radiation daily, by Eschenbrenner, Miller & Lorenz (126) had a sharp decrease in testis weight after two and four months of irradiation. The weight curves leveled off at different values for the different dose rates. The amount of interstitial tissue increased relatively, but not proportionately, to the decrease in testis weight. Mice receiving 1.1 and 4.4 r daily for as long as 16 months had a normal proportion of cells in different stages of spermatogenesis. This was normal in those receiving 8.8 r daily for 4 months, while after 6 months of irradiation there was failure of completion of spermatogenesis associated with Sertoli cell degeneration. Robinson & Engle (127) find a temporary cessation of spermatogenesis in a case of neutron bombardment involving human testes. The dose is unknown. Essenberg (128) reports response of x-rayed mouse ovaries to gonadotropins and pituitary gland implantations by germ cell proliferation from the germinal epithelium. Van Eck-Vermande & Freud (129) feel that the effect of gonadotropins on irradiation damaged mouse ovaries is more evident on the reduction of damage shown by follicles developing subsequent to the irradiation.

Furth (130) postulates that x-radiation of young female mice produces a hormonal unbalance, which along with a delayed radiation effect, brings about the development of ovarian tumors. Radiation produced amenorrhea was found to be of nonovarian origin by Goldscheider (131) and is possibly due to destruction of uterine glands.

In studying the responses of the rat pituitary to radiation,

Freed & co-workers (132) found that low doses of x-rays (100 to 200 r) did not affect the estrus cycle of the rat and therefore produce at best only transient injury to the pituitary. According to Leitch *et al.* (133), low daily doses (3 n) of neutrons, however, disrupted the estrus cycle of rats as well as retarding the growth and temporarily reducing the number of white cells.

Baidins *et al.* (134) found that doses of 2 to 1,000 r of x-rays to the normal infantile rat pituitary do not interfere with its normal gonadotrophic function. While estradiol had no effect, estradiol treatment followed by x-rays resulted in degenerative changes in ovarian follicles. There was a significant increase in ovarian weight due to increased development of interstitial tissue. The pituitaries showed no histological differences. Gorbman (135) finds that large doses of radioiodine administered to mice result in pituitary growths evident 250 days after the  $I^{131}$  injection. Patt *et al.* (136) found radiation toxicity potentiated in hypophysectomized rats.

The similarity between the symptoms of radiation sickness and the general adaptation syndrome is mentioned by several authors including Prosser (137), Edelmann (138), Ellinger (139), Cronkite & Chapman (140), and evidence relating adrenal cortical activity to the two syndromes is presented by North & Nims (141) who show that adrenal cholesterol, adrenal ascorbic acid and liver glycogen of fasted rats respond to x-irradiation in a fashion similar to other stresses.

Further evidence of adrenal cortical response is seen in the increased urinary 17-ketosteroid excretion following radiotherapy, as shown by Davison *et al.* (142). Schwartz reports (143) an increased amount of "corticosteroid-like" substances in patients after radiotherapy. The mitotic index of the adrenal cortex increases after radiation, according to Knowlton & Hempelmann (144). Hypophysectomy as shown by Patt *et al.* (136) in the rat, appears to prevent the changes in adrenal chemistry which ordinarily result from exposure to x-rays.

A transient increase in SCN space was found by France (145) in rats and mice following sublethal doses of x-irradiation. At lethal levels of radiation the relative muscle and plasma water and plasma volume increased despite a negative water balance. Animals dehydrated by dietary water restriction lived longer following radiation than controls. Edelmann (146) observed that rats im-

bibed and excreted large amounts of fluids (water and 1 per cent sodium chloride solution) on the first and fifth 24 hour period following x-irradiation. Urinary excretions of sodium, potassium, and chlorine were increased at these times. Changes in the chylomicrograph and the chylomicron count related to time, were noted by Setala & Ermala during radiation sickness. Similar changes occur after histamine administration (147).

Histamine and histamine-like substances have been postulated as one of, if not the toxic agent in radiation sickness. The evidence for this is reviewed by Ellinger (139) who has advanced this theory. Weber & Steggerda found histamine in the blood of rats given 600 r of x-irradiation two hours and five days previously (148). In humans desoxycorticosterone acetate (DOCA) was found by Ellinger *et al.* (149) to have some effect on the nausea and vomiting resulting from radiotherapy. This was attributed to the antihistamine properties of DOCA. A potent antihistaminic was found to be of no value in radiation sickness therapy by Brown & Hunter (150). Mains (151), however, finds skin ointments containing antihistamine substances beneficial in preventing, at least in part, skin reactions to radiations.

Patients with nausea and vomiting following radiotherapy showed low niacin and riboflavin excretions and B-complex vitamins had a beneficial effect in treating these aspects of radiation sickness (152).

Brues (153) reports severe cell damage and liver atrophy following injections of small amounts of plutonium. Ellinger (154) reports that DOCA protects the liver against radiation-induced fatty changes.

A temporary increase in ribonucleic acid concentration of rat liver was noted by Petrakis *et al.* during the first 24 hr. following x-irradiation, followed by a decrease below normal at two and six days. Nuclear desoxyribosenucleic acid was also decreased at two and six days (155). Ely & Ross found these nucleic acids to be decreased from 4 hr. to 17 days following x-irradiation (156) and from 4 to 48 hr. after neutron radiation (157). Evidence that the rate of formation of desoxyribosenucleic acid is reduced by radiation is furnished by Hevesy (158).

Reduction in the intestinal stroma is reported by Ely & Ross after both x- (156) and neutron (157) irradiation. Atrophy of the

gastric mucosa, preceded by hyperemia, hemorrhage and edema was seen after roentgen irradiation by Ricketts, *et al.* (159). Knowlton & Hempelmann (144) have reported an increase in mitotic activity of the jejunum after irradiation.

A flaccid paralysis of the lower extremities without sensory loss was noticed by Greenfield & Stark in three of 180 cases treated by x-irradiation of the testes. The syndrome termed "post-hyphenate irradiation neuropathy" is believed to be caused by injury of the anterior horn cells in the lumbosacral segments of the spinal cord (160). Radiation to the head may result in brain necrosis related to reactions of the smaller blood vessels, according to Pennybacker & Russell (161). A discussion of the treatment of pain by x-rays is given by Dufresne (162).

With the use of radiotherapy in ophthalmology, Hughes & Iliff point out that the sensitivities of the various normal and pathological tissues must be known. Direct irradiation over the cornea must be performed with care because of the great sensitivity of the corneal epithelium (163). This subject has been reviewed by Enloe (164).

In experiments performed by Warren & Dixon (125) bone growth was retarded in young chicks receiving injections of  $P^{32}$ . The cartilage cells of the epiphyses were more sensitive than the osteoblasts and osteoclasts. After the radiation ceased, the histology returned to normal but the bones remained dwarfed.

The epiphyses of the vertebral bodies of young rabbits may be suppressed by 700 to 1,000 r of x-radiation. Unilateral application yielded greater effects on the irradiated side, according to Arkin, Simon & Siffert (165). Similar inhibition of skeletal growth is reported by Cupp, Kohn & Stapleton following externally applied local beta irradiation to rats (166). Neuman *et al.* (167) report that the resorptive processes of bone are inhibited by the radiation from uranium and not its specific chemical action.

According to Chase (168) the amount of greying of hair of strain C-57 mice caused by x-radiation depends upon the stage of follicle development at time of irradiation. This may be associated with relative differences in melanoblast population at the various stages. Pohle, Ritchie & Moir found no microscopic or macroscopic effects of x-radiation on the healing of wounds in the skin of white rats (169). Evidence that metabolic activity rather

than body temperature is important in increasing the mortality of x-rays is presented by Blount & Smith (170). The physical performance of rats, measured by exhaustive swimming tests, was decreased by 600 r of x-rays (171) as reported by Kimeldorf *et al.*

The author has, with only one exception, confined this review to ionizing radiation and those of its effects which he deems of practical or theoretical interest to physiologists. Many articles have appeared which were judged to be in the realm of genetics and were therefore not reviewed here. A large number of reports were considered clinical in nature and were felt to be of insufficient interest to physiologists to warrant space in this volume. While no one is able to state whether or not tracer amounts of radioactive isotopes produce a radiation effect, those experiments in which isotopes were used primarily as tracers were omitted.

## LITERATURE CITED

1. *Histopathology of Irradiation from External and Internal Sources*, 808 pp. (Bloom, W., Ed., McGraw-Hill Co., New York, 1948)
2. *Biological and Medical Effects of High Energy Radiation, II*, Part II. "An International Bibliography on Atomic Energy, Scientific Aspects" (United Nations Atomic Energy Commission, Lake Success, New York, 1948)
3. *Isotopes in Biology and Medicine, II*, Part IV. "An International Bibliography on Atomic Energy, Scientific Aspects" (United Nations Atomic Energy Commission, Lake Success, New York, 1948)
4. LAWRENCE, J. H., AND HAMILTON, J. G., in *Advances in Biological and Medical Physics* (Academic Press, Inc., New York, 1948)
5. Radioiodine, *Brookhaven Natl. Lab. Conf. Rept.*, BNL-C-5, 114 pp. (Upton, New York, 1948)
6. Biological Applications of Nuclear Physics, *Brookhaven Natl. Lab. Conf. Rept.* BNL-C-4, 154 pp. (Upton, New York, 1948)
7. DOWDY, A. H., *Atomic Energy Commission Declassified Document No. AECU-353* (1949)
8. WOLF, B. S., *Nucleonics*, **3**, 25-29 (1948)
9. GORMAN, A. E., *Civil Eng.*, **19**, 29-32 (1949)
10. GORMAN, A. E., AND WOLMAN, A., *Am. J. Pub. Health*, **39**, 443-54 (1949)
11. WESTERN, F., *Nucleonics*, **3**, 43-49 (1948)
12. BEERS, N. R., *Nucleonics*, **4**, 28-38 (1949)
13. FAILLA, G., *Atomic Energy Commission Declassified Document No. AECD-2362* (1942)
14. NICKSON, J. J., *Atomic Energy Commission Declassified Document No. AECD-2424* (1946)
15. WILLIAMS, C. R., *J. Ind. Hyg. Toxicol.*, **30**, 294-99 (1948)
16. CHAMBERLAIN, W. E., NEWELL, R. R., TAYLOR, L. T., AND WYCKOFF, H., *Am. J. Roentgenol. Radium Therapy*, **61**, 726-28 (1949)
17. GOLDSMITH, H. H., *Nucleonics*, **4**, 62-69 (1949)
18. BARILLET, F., *L'Ind. Chim. et Phosphate Reunis*, **35**, 123-28 (1948)
19. GERMAN, L. L., AND ROZENDAAL, H. M., *Elec. Eng.*, **67**, 884-90 (1948)
20. HOWARTH, F., *Lancet*, **II**, 51-53 (1948)
21. EAMES, R. P., *Safety Eng.*, **96**, 26-30 (1948)
22. MORGAN, K. Z., *J. Southeast. Research*, **1**, 6-10 (1948)
23. MORGAN, G. W., *Proc. Auburn Conf. on Use of Radioactive Isotopes in Agr. Research*, 54-69 (1948)
24. *Radiological Safety Regulations*, No. NP-622, 95 pp. (Navy Dept., Bureau of Med. & Surg., Washington, D. C., 1947)
25. *Atomic Energy Commission Declassified Document No. AECU-168* (1948)
26. MORGAN, K. Z., *J. Ind. Hyg. Toxicol.*, **30**, 286-93 (1948)
27. LAPP, R. E., AND ANDREWS, H. L., *Nucleonics*, **3**, 60-67 (1948)
28. WARREN, S., AND BOWERS, J. Z., *Am. J. Pub. Health*, **39**, 654-57 (1949)
29. BARNES, E. C., *Industry and Power*, **56**, 87 (1949)
30. CHAMBERLAIN, W. E., NEWELL, R. R., TAYLOR, L. T., AND WYCKOFF, H., *J. Am. Med. Assoc.*, **138**, 818-19 (1948)

31. Introductory manual on the control of health hazards from radioactive materials prepared for the Medical Research Council for the Ministry of Supply, *Atomic Energy Research Establishment, Issue No. 2*, 15 pp. (Gt. Brit. Ministry of Supply, Med. Research Council, 1949)
32. BRYAN, F. A., *Ind. Med.*, **17**, 367-71 (1948)
33. STAUFFER, H. M., *X-ray Technician*, **20**, 219-22, 239 (1949)
34. HO, T. J., *X-ray Technician*, **20**, 353-55 (1949)
35. *Recommendations of the British X-ray and Radium Protection Committee, 7th Rept.*, 16 pp. (London, 1948)
36. BRAESTRUP, C. B., AND WYCKOFF, H. O., *Radiology*, **51**, 840-48 (1948)
37. Editorial, *J. Am. Med. Assoc.*, **138**, 214-15 (1948)
38. PERRY, C. H., *Atomic Energy Commission Declassified Document No. AECU-3-6*, (1949)
39. SKANSE, B. N., *J. Clin. Endocrinol.*, **8**, 707-16 (1948)
40. LUKENS, R. M., *Ann. Otol. Rhinol & Laryngol.*, **57**, 633-42 (1948)
41. SALISBURY, W. W., CLARK, J. W., AND HINES, H. M., *Electronics*, **22**, 66-67 (1949)
42. EVANS, T. C., *Nucleonics*, **4**, 2-8 (1949)
43. SNIDER, C., *Atomic Energy Commission Declassified Document No. AECD-2326* (1947)
44. NORRIS, W. P., *Ind. Eng. Chem.*, **41**, 231-32 (1949)
45. LEVY, H. A., *Atomic Energy Commission Declassified Document No. AECD-2549-H* (1948)
46. MORGAN, G. W., *Nucleonics*, **4**, 24-37 (1949)
47. HUGHES, H. A., *Electronic Eng.*, **21**, 80-86 (1949)
48. COHEN, L., *Brit. J. Radiology*, **22**, 160-63 (1949)
49. BUSH, F., *Brit. J. Radiology*, **22**, 96-105 (1949)
50. BRAESTRUP, C. B., CAMERON, G. H., AND McCLEMENT, P., *Am. J. Roentgenol. Radium Therapy*, **61**, 397-401 (1949)
51. *Report on Qualitative Specifications for Animal Laboratories for Experimental Work with Radioactive Materials to Brookhaven National Laboratory*, 82 pp. (Arthur D. Little, Inc., Cambridge, Mass., 1948)
52. CASSEN, B., AND CURTIS, L., *Atomic Energy Commission Declassified Document No. AECD-2447* (1948)
53. WAHLBERG, T., *Acta Radiol.*, **30**, 291-98 (1948)
54. DESSAUER, G., AND LENNOX, E., *Atomic Energy Commission Declassified Document No. AECD-2278* (1944)
55. DUDLEY, R. A., AND DOBYNS, B. M., *Science*, **109**, 327-28 (1949)
56. TOBIAS, C. A., AND DUNN, R. W., *Science*, **109**, 109-13 (1949)
57. BOYD, G. E., *Atomic Energy Commission Declassified Document No. AECD-2507* (1949)
58. *J. Roy. Army Med. Corps*, **91**, 219-38 (1948)
59. *Bull. U. S. Army Med. Dept.*, **8**, 350-56 (1948)
60. *Bull. U. S. Army Med. Dept.*, **8**, 357-62 (1948)
61. *Bull. U. S. Army Med. Dept.*, **8**, 422-28 (1948)
62. *Bull. U. S. Army Med. Dept.*, **8**, 428-31 (1948)
63. *Bull. U. S. Army Med. Dept.*, **8**, 431-33 (1948)

64. *Bull. U. S. Army Med. Dept.*, **8**, 511-17 (1948)
65. *Fire Eng.*, **101**, 674-78 (1948)
66. *Atomes*, **3**, 244 (1948)
67. PRICE, F. L., *Florida Med. Assoc.*, **34**, 651-53 (1948)
68. PARSONS, R. P., *Am. J. Surg.*, **76**, 559-62 (1948)
69. LOONEY, W. B., *Virginia Med. Monthly*, **76**, 73-75 (1949)
70. KESTER, W. O., AND MILLER, E. B., *J. Am. Vet. Med. Assoc.*, **113**, 325-29 (1948)
71. KESTER, W. O., AND MILLER, E. B., *J. Am. Vet. Med. Assoc.*, **114**, 113-19 (1949)
72. COX, W. C., *Bull. U. S. Med. Dept.*, **8**, 862-76 (1948)
73. BAUER, A. J., *Delaware State Med. J.*, **20**, 121-23 (1948)
74. LUETH, H. C., *Illinois Med. J.*, **94**, 93-99 (1948)
75. BONET-MAURY, P., AND LEFORT, M., *Nature*, **162**, 381-82 (1948)
76. BARRON, E. S. G., DICKMAN, S., MUNTZ, J. A., AND SINGER, T. P., *J. Gen. Physiol.*, **32**, 537-52 (1949)
77. BARRON, E. S. G., AND DICKMAN, S., *J. Gen. Physiol.*, **32**, 595-605 (1949)
78. BARRON, E. S. G., *Atomic Energy Commission Declassified Document No. AECD-2316* (1946)
79. ZIRKLE, R. E., *Radiology*, **52**, 846-55 (1949)
80. MAZIA, D., AND BLUMENTHAL, G., *Proc. Natl. Acad. Sci. U. S.*, **34**, 328-36 (1948)
81. KRENZ, F. H., *Can. J. Research*, [B]**26**, 647-56 (1948)
82. ALPER, T., *Nature*, **162**, 615-16 (1948)
83. PROCTOR, B. E., AND GOLDBLITH, S. A., *Nucleonics*, **3**, 32-43 (1948)
84. MILLER, N., *Nature*, **162**, 448-49 (1948)
85. TAYLOR, B., GREENSTEIN, J. P., AND HOLLAENDER, A., *Arch. Biochem.*, **16**, 19-31 (1948)
86. MATHIS, A. L., BROOKS, R. E., AND SCHNEIDERMAN, H., *Atomic Energy Commission Declassified Document No. AECU-170* (1949)
87. POLLARD, E. C., AND FORRO, F., JR., *Science*, **109**, 374-75 (1949)
88. DALE, W. M., GRAY, L. H., AND MEREDITH, W. J., *Trans. Roy. Soc. (London)*, [A] **242**, 33-62 (1949)
89. SOMMERMEYER, K., *Z. Naturforsch.*, **3b**, 57-59 (1948)
90. VAN DER WERFF, J. T., *Biological Reactions Caused by Electric Currents and X-rays* (Elsevier Publishing Co., New York, 1948)
91. BONHAM, K., *Atomic Energy Commission Declassified Document No. AECU-309* (1949)
92. BONHAM, K., DONALDSON, L. R., FOSTER, R. F., WELANDER, A. D. AND SEYMOUR, A. H., *Growth*, **12**, 107-21 (1948)
93. WELANDER, A. D., DONALDSON, L. R., FOSTER, R. F., BONHAM, K., SEYMOUR, A. H., AND LOWMAN, F. G., *Atomic Energy Commission Declassified Document No. AECU-188*
94. TANSLEY, K., GRAY, L. H., AND SPEAR, F. G., *Brit. J. Radiology*, **21**, 567-70 (1948)
95. MURRAY, R., PIERCE, M., AND JACOBSON, L. O., *Atomic Energy Commission Declassified Document No. AECD-2303* (1948)

96. DIXON, F. J., *Proc. Soc. Exptl. Biol. Med.*, **68**, 505-7 (1948)
97. BRECHER, G., ENDICOTT, K. M., GUMP, H., AND BRAWNER, H. P., *Blood*, **3**, 1259-74 (1948)
98. SMITH, W. W., DOOLEY, R., AND THOMPSON, E. C., *J. Aviation Med.*, **19**, 227-37 (1948)
99. JACOBSON, L. O., AND SIMMONS, E. L., *Atomic Energy Commission Declassified Document No. AECD-2372* (1946)
100. CRONKITE, E. P., ULLRICH, F. W., ELTZHOLTZ, D. C., SIPE, C. R., AND SCHORK, P. K., *Rept. No. 21, Naval Med. Research Inst. Project NM-007-039* (1949)
101. LOW-BEER, B. V. A., AND STONE, R. S., *Atomic Energy Commission Declassified Document No. AECD-2348* (1948)
102. NICKSON, J. J., *Atomic Energy Commission Declassified Document No. AECD-2432* (1947)
103. PRICE, C. H. G., *Brit. J. Radiology*, **21**, 481-93 (1948)
104. BOURRET, J., *Deut. med. Wochschr.*, **74**, 447 (1949)
105. JACOBSON, L. O., MARKS, E. K., GASTON, E., ALLEN, J. G., AND BLOCK, M. H., *J. Lab. Clin. Med.*, **33**, 1566-78 (1948)
106. HOLDEN, W. D., COLE, J. W., PORTMANN, A. F., AND STORAASLI, J. P., *Proc. Soc. Exptl. Biol. Med.*, **70**, 553-56 (1949)
107. JACOX, H. W., *Radiology*, **51**, 860-61 (1948)
108. CLARK, W. G., UNCAPHER, R. P., AND JORDON, M. L., *Science*, **108**, 629-30 (1948)
109. FIELD, J. B., AND REKERS, P. E., *Atomic Energy Commission Declassified Document No. AECU-149* (1949)
110. CRONKITE, E. P., ELTZHOLTZ, D. C., SIPE, C. R., CHAPMAN, W. H., AND CHAMBERS, F. W., *Proc. Soc. Exptl. Biol. Med.*, **70**, 125-28 (1949)
111. KOHN, H. I., ROBINETT, P. W., AND CUPP, M. N., *Atomic Energy Commission Declassified Document No. AECD-2176* (1948)
112. HERVÉ, A., AND LECOMTE, J., *Arch. intern. pharmacodynamie*, **79**, 109-12 (1949)
113. SHORVON, L. M., *Brit. J. Radiology*, **22**, 49-55 (1949)
114. STEARNER, S. P., *Proc. Soc. Exptl. Biol. Med.*, **69**, 518-21 (1948)
115. ADAMS, W. S., AND LAWRENCE, J. S., *Am. J. Med. Sci.*, **216**, 656-60 (1948)
116. CRONKITE, E. P., TULLIS, J. L., TESSMER, C., AND ULLRICH, T. W., *Naval Med. Research Inst. Rept. No. 18*, 12 pp. (1948)
117. LAWRENCE, J. S., DOWDY, A. H., AND VALENTINE, W. N., *Radiology*, **51**, 400-13 (1948)
118. ROSENTHAL, R. L., *Atomic Energy Commission Declassified Document No. AECU-105* (1949)
119. DE BRUYN, P. P. H., *Anat. Record*, **101**, 373-405 (1948)
120. DOWNEY, H., *Blood*, **3**, 1315-41 (1948)
121. SCHREK, R., *Am. J. Path.*, **24**, 1055-64 (1948)
122. CRADDOCK, C. G., JR., AND LAWRENCE, J. S., *J. Immunol.*, **60**, 241-54 (1948)
123. CRADDOCK, C. G., JR., VALENTINE, W. N., AND LAWRENCE, J. S., *J. Lab. Clin. Med.*, **34**, 158-77 (1949)
124. STURKIE, P. D., PINO, J. A., WEATHERWAX, J. L., DONNELLY, A. J., AND DORRANCE, G. M., *Radiology*, **52**, 112-17 (1949)

125. WARREN, S., AND DIXON, F. J., *Radiology*, **52**, 714-29 (1949)
126. ESCHENBRENNER, A. B., MILLER, E., AND LORENZ, E., *J. Natl. Cancer Inst.*, **9**, 133-47 (1948)
127. ROBINSON, J. N., AND ENGLE, E. T., *J. Urol.*, **61**, 781-84 (1949)
128. ESSENBERG, J. M., *Western J. Surg. Obstet. Gynecol.*, **57**, 61-66 (1949)
129. VAN ECK-VERMANDE, G. J., AND FREUD, J., *Arch. intern. pharmacodynamie*, **78**, 67-78 (1949)
130. FURTH, J., *Proc. Soc. Exptl. Biol. Med.*, **71**, 274-77 (1949)
131. GOLDSCHIEDER, G., *Lancet*, **I**, 521-23 (1949)
132. FREED, J. H., FARRIS, E. J., MURPHY, D. P., AND PENDERGRASS, E. P., *J. Clin. Endocrinol.*, **8**, 461-81 (1948)
133. LEITCH, J. L., GAY, D. M., AND NEVILLE, G. A., *Am. J. Roentgenol. Radium Therapy*, **61**, 530-33 (1949)
134. BAIDENS, A., CLAESSON, L., AND WESTMAN, A., *Acta Endocrinol.*, **1**, 133-40 (1948)
135. GORBMAN, A., *Proc. Soc. Exptl. Biol. Med.*, **71**, 237-40 (1949)
136. PATT, H. M., SWIFT, M. N., TYREE, E. B., AND STRAUBE, R. L., *Science*, **108**, 475-76 (1948)
137. PROSSER, C. L., in "Biological Applications of Nuclear Physics," 36-39, *Brookhaven Natl. Lab. Conf. Rept. No. BNL-C-4* (Upton, New York, 1948)
138. EDELMANN, A., in "Biological Applications of Nuclear Physics," 72-77, *Brookhaven Natl. Lab. Conf. Rept. No. BNL-C-4*, (Upton, New York, 1948)
139. ELLINGER, F., in "Biological Applications of Nuclear Physics," 59-65, *Brookhaven Natl. Lab. Conf. Rept. No. BNL-C-4*, (Upton, New York, 1948)
140. CRONKITE, E. P., AND CHAPMAN, W. H., *Military Surgeon*, **104**, 7-21 (1949)
141. NORTH, N., AND NIMS, L. F., *Federation Proc.*, **8**, 119-20 (1949)
142. DAVISON, R. A., KOETS, P., AND KUZELL, W. C., *J. Clin. Endocrinol.*, **9**, 79-88 (1949)
143. SCHWARTZ, S., *Bull. Univ. Minn. Hosp.*, **20**, 617-54 (1949)
144. KNOWLTON, N. P., JR., AND HEMPELMANN, L. H., *J. Cellular Comp. Physiol.*, **33**, 73-91 (1949)
145. FRANCE, O., *Atomic Energy Commission Declassified Document No. AECU-131* (1946)
146. EDELMANN, A., *Federation Proc.*, **8**, 39 (1949)
147. SETALA, K., AND ERMALA, P., *Ann. Chir. Gynaecol. Fenniae*, **37**, Suppl. 1, 1-60 (1948)
148. WEBER, R. P., AND STEGGERDA, F. R., *Proc. Soc. Exptl. Biol. Med.*, **70**, 261-63 (1949)
149. ELLINGER, F., ROSWIT, B., AND GLASSER, S. M., *Am. J. Roentgenol. Radium Therapy*, **61**, 387-96 (1949)
150. BROWN, W. M. C., AND HUNTER, R. B., *Brit. Med. J.*, 984 (1948)
151. MAINS, M. P., *Radiology*, **52**, 579-81 (1949)
152. JARVIS, J. L., AND CAYER, D., *Radiology*, **52**, 574-78 (1949)
153. BRUES, A. M., "Effect of Plutonium on the liver," *Trans. 7th Conf. on Liver Injury*, 59-61 (New York, April, 1948)

154. ELLINGER, F., *Radiology*, **50**, 234-42 (1948)
155. PETRAKIS, N. L., ASHLER, F. M., AND FERKEL, R. L., 18 pp. *Naval Radiol. Defense Lab. Rept. AD-126* (1949)
156. ELY, J. O., AND ROSS, M. H., *Cancer Research*, **8**, 285-94 (1948)
157. ELY, J. O., AND ROSS, M. H., *Cancer Research*, **8**, 607-12 (1948)
158. HEVESY, G., *Nature*, **163**, 869-70 (1949)
159. RICKETTS, W. E., KIRSNER, J. B., HUMPHREYS, E. M., AND PALMER, W. L., *Gastroenterology*, **11**, 818-32 (1948)
160. GREENFIELD, M. M., AND STARK, F. M., *Am. J. Roentgenol. Radium Therapy*, **60**, 617-22 (1948)
161. PENNYBACKER, J., AND RUSSELL, D. S., *J. Neurol. Neurosurg. Psychiat.*, **11**, 183-98 (1948)
162. DUFRESNE, O., *Can. Med. Assoc. J.*, **60**, 227-29 (1949)
163. HUGHES, W. F., JR., AND ILIFF, C. E., *Am. J. Ophthalmology*, **32**, 351-60 (1949)
164. ENLOE, C. F., *Sight-Saving Rev.*, **18**, 77-83 (1948)
165. ARKIN, A., SIMON, N., AND SIFFERT, R., *Proc. Soc. Exptl. Biol. Med.*, **69**, 171-73 (1948)
166. CUPP, M. N., KOHN, H. I., AND STAPLETON, G. E., *Atomic Energy Commission Declassified Document No. AECD-2219* (1948)
167. NEUMAN, W. F., NEUMAN, M. W., AND MULRYAN, B. J., *Atomic Energy Commission Declassified Document No. AECD-2580* (1949)
168. CHASE, H. B., *J. Morphol.*, **84**, 57-76 (1949)
169. POHLE, E. A., RITCHIE, G., AND MOIR, W. W., *Radiology*, **52**, 707-13 (1949)
170. BLOUNT, H. C., JR., AND SMITH, W. W., *Science*, **109**, 83-84 (1949)
171. KIMELDORF, D. J., JONES, D. C., GONZALEZ, T. A., LEE, J. L., AND FISHLER, M. C., 21 pp., *Naval Radiol. Defense Lab. Interim Rept. No. AD-117 (B)* (1949)
172. LEA, D. E., *Action of Radiations on Living Cells*, 402 pp. (1946, Cambridge University Press, England)

## PHYSIOLOGICAL GENETICS<sup>1</sup>

By D. G. CATCHESIDE

*Botany School, University of Cambridge, Cambridge, England*

Genetics has developed such a diversity of interests and of contacts with other disciplines that it is difficult to cover, let alone do justice to, the numerous contributions that have appeared in the last two years. The present review is, therefore, limited particularly to those aspects of genetics which, being of interest to the writer, appear to constitute significant or promising developments towards a knowledge of how the gene is constituted, reproduces, and controls development and differentiation.

The report of the first postwar international genetics congress, the eighth in the series held last year, has been published (1). Under the editorship of Demerec, a new review journal, *Advances in Genetics*, has commenced publication. The first two volumes contain articles of physiological interest, namely, Sonneborn (2a) on protozoan genetics, Irwin (2b) on immunogenetics, Caspari (3a) on cytoplasmic inheritance, and Heston (3b) on the genetics of cancer. Several volumes bearing on the relation of genetics to medicine have appeared, including the Messenger lectures by Muller, Little & Snyder (4), the books by Grüneberg (5), Crew (6), and the symposium (7) on the genetics of cancer organised by the Genetical Society and the British Empire Cancer Campaign. The second of the annual volumes of the *Symposia of the Society of Experimental Biology* is titled *Growth* (8). It contains several articles on genetic aspects of the problem of growth. In a recent volume, Mather (9) has gathered together his ideas of the treatment of quantitative inheritance. The problem of nucleic acid has been the subject of another symposium (10), which is interesting to compare with the previous British one. Lindegren (11) has produced a substantial volume on his studies of yeast genetics.

The following reviews of special subjects have appeared. Lederberg (12) has surveyed the problems and methods of microbial genetics. Burnet & Fenner (13) have reviewed the relation of genetics and immunology. L'Heritier (14) has published a full account of the behaviour of the viroid, or cytoplasmic particle responsible for carbon dioxide sensitivity in *Drosophila*.

<sup>1</sup> This review covers the period from 1947 to 1949.

*Mutagenic agents.*—Auerbach (15) has recently reviewed the state of knowledge of chemical mutagens. Since mustard gas and related compounds were shown to be mutagenic, a wide variety of other chemicals have been found to have similar properties in at least some measure. These include several carcinogenic substances (1, 16, 17), sodium desoxycholate and acriflavin (1, 18), caffeine and theophylline (19), some phenols and related compounds (20) and urethane (1, 21). Oehlkers (21a) reports a cytoplasmic influence on the effectiveness of chemical mutagens. Formaldehyde added to the food of *Drosophila* in sublethal concentrations strikingly increases the mutation rate (22).

More experiments with combination treatments have been reported to show effects greater than additive. These include x-radiation with various chemical treatments (23), mustard gas and neutrons (24), nitrogen mustard followed by ultraviolet radiation (25), and infrared radiation with nitrogen mustard (26).

Darlington & Koller (27) find the effects of mustard gas on *Tradescantia* chromosomes to be similar to those of x-rays of low intensity. Ford's experiments (27a), however, suggest a different distribution of breaks.

There is some evidence (24) of the preferential appearance of certain mutants following nitrogen mustard treatment, but, as a whole, the various mutagens seem to be quite nonspecific.

*Production and detection of biochemical mutations.*—The desire of all geneticists and biochemists working with microorganisms is to find more efficient techniques for the discovery of mutants with increased growth factor requirements. The filtration technique devised by Fries (28) has proved to be unsatisfactory for *Neurospora*. However, Lein, Mitchell & Houlahan (29) have devised a different improved method for *Neurospora*. It consists in spermatizing petri plate cultures with irradiated conidia of the opposite sex. When the perithecia are ripe and ascospores are being shed, samples of the ascospores are collected by inverting the plate containing perithecia over a second plate containing minimal or other selective agar medium. When a suitable spore deposit has been secured, with spores not less than 1 mm. apart, the plate is incubated and later inspected for clusters of small colonies. These are transferred to individual tubes and further tested. By this means, three mutants requiring histidine, tryptophane, or methionine respectively, and not previously found, were obtained. None of

these mutants will grow on "complete" medium, and it seems possible that many groups of mutants may not be obtained because of growth inhibition by constituents of the medium used for isolations.

Westergaard & Mitchell (30) have devised a medium that favours the sexual reproduction of *Neurospora*. Emerson (31) has found that furfural will activate ascospores to germinate almost as well as the standard heat treatment. Various substances, such as sodium desoxycholate and the detergent Tergitol, or the substitution of sorbose for the other sugar in the medium, have been found by Tatum, Barratt & Cutter (32, 33) to result in the formation of small, nonspreading colonies. It seems possible that the use of such substances to induce colonial paramorphic effects in filamentous fungi may permit the application of Lederberg & Tatum's double plate enrichment technique (34) to such fungi. Meyersburg, Pomper & Cutter (35) describe a photographic technique to assist in the detection of putative biochemical mutants in such plates. Pontecorvo (36) has given an account of auxanographic techniques applied to biochemical genetics.

Fries (37, 38) has found a starvation technique which serves to concentrate nutritional mutations in *Ophiostoma*. It consists in keeping conidia suspended in deficient liquid medium for a considerable time and then plating out dilutions of the suspension. Mutants appear to retain viability longer than the wild type under these conditions.

In the case of bacteria, Davis (39) has described a method of isolation employing limited enrichment of the medium. This method avoids the slow growers and normals with delayed growth and also guards against the death of fragile mutants through starvation. A remarkable increase in the efficiency of isolation of mutants has been secured by means of penicillin (40). Treated bacteria are first incubated in complete medium, so that mutants with a lag phase may become expressed. The cells are then thoroughly washed and resuspended in suitable dilutions in minimal medium in the presence of penicillin. The normals, able to grow on the minimal medium, are killed by the penicillin; but the mutants which cannot grow remain viable. After a suitable interval, the cells are thoroughly washed, plated on a complete or a selective medium, and the colonies isolated. Close to 100 per cent of these colonies are found to be biochemically-deficient mutants.

*Mechanism of gene action and nature of gene mutation.*—In the *Neurospora* investigations, two cases of enzyme control by specific genes have been found. Mitchell & Lein (41, 42) have obtained a mutant that is unable to couple indole and serine to produce tryptophane. Neither the living mycelium nor the cell-free extracts will accomplish this synthesis. The other case shows some remarkable features. Wagner & Guirard (43) found that intact mycelia of a pantothenicless mutant were unable to produce pantothenate from pantoyl lactone and  $\beta$ -alanine. Later, Wagner (44) found that this mutant and another allele of it have, like the wild type, an enzyme system for this synthesis *in vitro*. The data rule out an enzyme absence hypothesis for these mutants, assuming that it is this particular step in pantothenate synthesis that is involved. The latter point could be demonstrated if a deficiency for the gene should be obtained. It is clear that we must be prepared to find allelic states of genes that produce enzymes which are inactive under all normal cellular conditions, but which become active when freed from the cellular environment. This would appear to be a different kind of inactivation from that found in the previously described cases of temperature-sensitive and pH-sensitive mutants in which the activity is suppressed by an environmental change.

The one gene-one enzyme hypothesis continues to attract attention, though there is little prospect of decisive evidence for or against it in the near future. Horowitz (45) has considered the relations of reparable and irreparable biochemical mutations amongs temperature sensitive mutations. Both types will grow on minimal at one part of the temperature range; the reparable mutants will grow at other parts of the temperature range if supplied with some component of the complete medium, while the irreparable mutants will grow neither in minimal nor complete at other temperatures. Their relative frequency allows the calculation of the frequency of genes with a single function as being at least 0.74. Bonner (46) has studied mutant strains of *Neurospora* unable to utilize lactose. Such strains lack the enzyme splitting lactose into glucose and galactose. The alteration of any one of two, and probably three, genes results in the loss of lactase production. The suggestion is made that enzymes are synthesized by characteristic sequential series of biochemical reactions. It may be noted that Lederberg (47) finds that in *Escherichia coli* any one of seven genes affects lactase production. Moreover, there are complex gene-enzyme pat-

terms suggesting that some mutants have indirect effects on the production of one or more enzymes.

In the case of multiple allelism, the possibility exists that various alterations of a given gene might lead to enzymes of various types or to one lacking the specificity. A less drastic alteration might give rise to an enzyme possessing specificity under certain environmental conditions and lacking it under others. All the evidence in *Neurospora* is indicative of the latter type. An alteration to a gene leading to an allele producing an enzyme with altered specificity, i.e., acting on a different substrate or producing a different product, would mean a block in the normal sequence of metabolic reactions and could lead to a viable organism only if the block was repairable or was in a sequence leading to a nonessential product or if the altered enzyme switched part of the metabolic sequence to or from part of another actual or potential one. The demonstration of the altered activity is most elusive.

Laughnan (48) has studied the alleles of the gene *A* in maize and found several properties of some of them that appear to be incompatible with a simple correspondence between the gene and a single primary reaction. *A* might appear to act by converting a precursor of a brown pigment into a precursor of a purple pigment (anthocyanin), its alleles differing in activity, were it not that certain alleles which are intermediate in effect show no dosage relations. Heterozygotes of these alleles with the allele  $A^{br}$  show a reduction in amount of anthocyanin and an increase in amount of brown pigment compared with  $A^{br}/a$  individuals, the *a* allele completely lacking anthocyanin. Another allele,  $a^p$ , shows a similar competitive effect in other combinations. Thirdly, several alleles, including those first mentioned, have a dominant, rather than recessive, brown pericarp effect. The alleles of South American origin appear to further the synthesis of both brown and purple pigment while those of North American origin act to convert their substrate only to a precursor of the purple pigment. The simplest hypotheses, capable of accounting for the data, imply a duality on the part of the genic agent, either in respect to one agent transforming one substrate into two different products, or two related substrates into two products, or else two agents transforming one substrate into two products. The differences between these hypotheses are almost purely formal and depend upon the degree of analysis applied to the agent and the specific reagents. In any event, it must

be that alleles of dual action are compound determinants whose components are closely, if not inseparably, linked.

Further evidence of the dual structure is provided by Laughnan (49) in showing that the origin of  $A^d$  alleles ( $A$ -dilute with pale purple plant and aleurone pigment and dominant brown pericarp) by mutation from  $A^b/a$  heterozygotes is accompanied by crossing-over in the region of the  $A$  gene. The conclusion appears to be that the  $A^b$  allele ( $A$ -brown with pale plant, dark aleurone, and dominant brown pericarp) is compound with a distal  $\beta$  component which has been lost in  $A^d$ . The possibility exists of finding the complementary  $a$  mutants with the dominant brown pericarp effect. Lindegren (49a) reports evidence in yeast of gene changes associated with crossing-over. Lewis (50, 50a) also has evidence of the dual nature of the incompatibility gene in *Oenothera organensis*. The numerous multiple alleles in this species conform in behavior to the typical *Nicotiana* oppositional allele system, in which the growth of a pollen tube carrying a given allele is more or less suppressed on any styles carrying the same allele, but on no other styles. Spontaneous mutations have been obtained by a convenient technique (50) and in all cases the alleles are self-compatible ones unlike the naturally occurring ones. Cross tests have shown that the mutant alleles lack the component whose presence in the pollen leads to an incompatibility reaction but still possesses the component whose presence in the style determines an incompatibility reaction. Thus, if  $S^6$  mutates to  $S^{6'}$  it is found that while  $\delta'$  pollen will grow on  $\delta'$  or  $\delta$  style, pollen bearing the normal  $\delta$  allele will grow neither on  $\delta'$  nor  $\delta$  styles. How the normally occurring alleles, no mutant origins of which have been observed, do arise is a complete mystery.

It has generally been assumed, and there has been little contradictory evidence, that induced mutations are similar to the spontaneously occurring ones. Stadler & Roman (51) have studied the properties of some x-ray induced mutations of the gene  $A$  in maize. Three, whose adverse effect on viability was the least, were selected for study from more than 250. All tests showed that the changes were more radical than the most extreme known spontaneous alleles. The induced changes appear to be deficiencies not only of the gene  $A$  but also of one or more neighboring ones.

This inability of x-rays to produce in maize induced mutations that are physiologically similar to spontaneously arising ones con-

flicts with reported experiences with other organisms such as *Drosophila*, fungi, and bacteria. It is most important that the evidence be closely scrutinized in each of these cases. Giles & Lederberg (52) have given fairly convincing evidence that ultraviolet light, x-rays, nitrogen mustard, and radioactive phosphorus ( $P^{32}$ ) will induce back mutations of nutritionally deficient strains to wild type. Some which revert spontaneously are induced to do so more readily. Others which have not been observed to revert spontaneously have been induced to do so. Finally there are some mutants, in which presumably the gene has been lost, which will not revert spontaneously or on irradiation. Different alleles of the same gene, namely, inositolless, differ more or less markedly in their rates of induced mutability to wild type (53, 54). Careful genetic tests have shown that the reversions are due to a genetic change at, or quite close to, the locus of the gene assumed to have reverted.

MacKinney & Jenkins (56) have studied with greater detail the carotenoids present in different fruit colour types in the tomato. In the absence of the gene *R*, the gene *T* is responsible (in yellow tomato) for pigment production on a limited scale, small amounts of lycopene invariably being present. In the absence of *T*, *R* (in tangerine tomato) leads to large quantities of prolycopene, all-trans- $\zeta$ -carotene, and poly-*cis*- $\psi$ -carotenes. With *R* and *T* together (in red tomato), these pigments or their immediate precursors are converted to lycopene and all-trans carotenes. Zechmeister & Went (55) draw attention to the significance of the gene *T* showing a stereochemical steering power directed towards a single structural type. Reference must also be made to the excellent work of Keitt, Leben & Shay (57) on the inheritance of pathogenicity in the fungus *Venturia inaequalis*.

*Genes and biosynthesis.*—In *Neurospora*, some further links in the study of tryptophane and of nicotinic acid synthesis have been obtained. Mitchell & Lein (42) describe a mutant that cannot produce the enzyme required to couple indole and serine to form tryptophane. This is the condensation inferred when it was found that the conversion of indole to tryptophane by an indoleless mutant was accompanied by a corresponding disappearance of serine from the medium (58). The hypothesis that nicotinic acid is normally formed from tryptophane has received some additional support from new mutants and a new precursor, 3-hydroxyanthranilic acid, of nicotinic acid has been recognised (59, 60). The

evidence suggests that the order of synthesis is anthranilic acid→indole→tryptophane→kynurenine→3-hydroxyanthranilic acid→nicotinic acid. One new mutant, described by Bonner (60), can utilise hydroxyanthranilic acid, but can utilise none of the preceding substances; another mutant, described by Mitchell, Houlahan & Lein (42), can utilise any of the above six substances. There are, however, discrepancies that are difficult to reconcile with this simple scheme. Thus there are mutants which accumulate anthranilic acid but which cannot use nicotinic acid, while other mutants that can use tryptophane, indole, anthranilic acid, or kynurenine cannot utilise 3-hydroxyanthranilic acid or nicotinic acid for growth. Moreover, using appropriate genetic stocks, it has proved impossible to detect conversion of tryptophane or kynurenine to 3-hydroxyanthranilic acid. Possibly the syntheses of tryptophane and of nicotinic acid are coupled rather than derived from one another.

Further progress in the elucidation of sulphur metabolism has been made. Homoserine has been shown (61) to be a precursor of methionine and of threonine. Coupled to cysteine, it forms cystathionine (62), from which homocysteine is cleaved and then methylated to form methionine. Other homoserine is converted to threonine,  $\alpha$ -aminobutyric acid being indicated as an intermediate by two mutants studied by Teas (63). It has been presumed that in *Neurospora*, as in other organisms, inorganic 6-valent sulphur is reduced to the 4-valent and then to the 2-valent state. Three mutants studied by Phinney (64) suggest that the reduction occurs after the sulphate has been coupled to an organic compound. The biosynthesis indicated is as follows: sulfate ion→cystic acid→cysteine sulphinic acid→cysteine. In each of the three mutants, one of the three reactions indicated is blocked.

Several genetically different mutants unable to synthesise lysine are known (65, 66). One (*ly-1*) can utilise  $\alpha$ -amino adipic acid in place of lysine, while the three others cannot, and so may be inferred to have blocks at a later stage of the synthesis. Two of the latter three mutants accumulate pyrimidine compounds, most probably uridine, when grown with limiting amounts of lysine. No accumulation occurs with the double mutant strain formed by combining one of them with *ly-1*, thus confirming the previous deduction that the *ly-1* block is the earliest of the four. The fact that pyrimidine accumulates when the biosynthesis of lysine is

obstructed at either of two points, while it does not accumulate when obstruction occurs at two other points, establishes an interdependence in the metabolism of pyrimidine and lysine. This interdependence is also strongly indicated by the fact that the introduction of a genetic block (pyrimidineless-3a, i.e., mutant No. 37301) into the series of reactions by which the pyrimidine ring is synthesised interferes with the utilisation by *ly-1* of the lysine precursor,  $\alpha$ -aminoadipic acid. This interference, shown by the double mutant *ly-1 pyr-3a*, persists when a third mutant gene, the specific suppressor of *pyr-3a* (67), is introduced to make the triple mutant *ly-1 pyr-3a su-pyr-3a*. The behaviour suggests that the utilisation of  $\alpha$ -aminoadipic acid is dependent upon the *pyr-3a* reaction.

Mutant alleles that possess a reduced activity under some circumstances, thus forming a partial block in the synthesis, provide a special kind of tool in the investigation of precursors. It is theoretically possible that the supply of additional amounts of compounds that come in a synthetic series at a position before a partial block could cause increased synthesis of the ultimate product and so increased growth of the mutant simply by a mass action effect. Mitchell & Houlahan (68) have applied this principle to a study of the temperature sensitive alleles pyrimidineless-3b and -3c and found that oxalacetic acid and some related compounds (aminofumaric acid and aminofumaric acid diamide) promote the growth of these "leaky" mutants but not that of other pyrimidineless mutants. They have also found (69) that some pyrimidineless mutants (for example, 38502), when grown in the presence of limiting amounts of cytidine, excrete orotic acid. This substance will substitute for uracil in supporting the growth of some other pyrimidineless mutants which on this evidence alone, assuming orotic acid was an intermediate in synthesis, would be taken to be later blocks in synthesis than 38502. However, double mutants, composed of 38502, and certain others (e.g., 37301) unable to utilise orotic acid, do not produce orotic acid. This establishes the fact that 38502 is a later rather than earlier block than 37301 and that orotic acid is formed by an irreversible side reaction from an unknown intermediate. By further utilising the partial block alleles of 37301, it has been shown that orotic acid can be converted to a precursor of the stage blocked in 37301.

Loring and his co-workers have continued their studies of pu-

rine- and pyrimidine-deficient mutants. They have one mutant that is deficient in guanine synthesis as well as adenine, guanine having a "sparing" action on the utilisation of adenine (70, 71). Guanosine or guanylic acid will substitute for guanine, while xanthine has a similar effect though with considerably lower maximum effect. They (72) also have a pyrimidineless mutant whose utilisation of pyrimidine ribonucleosides and ribonucleotides is completely inhibited by adenosine or adenosinetriphosphate, the former being the more effective. Fries (73) has a guanine-deficient mutant of *Ophiostoma* whose growth in guanine or guanosine is antagonised by hypoxanthine and adenine. On the other hand xanthine has a sparing action on the utilisation of guanine.

Lewis (74) has studied a number of mutants that require a supplement of a carboxylic acid. All except one are genetically and biochemically alike. The one most studied requires a supplement of succinic acid or any one of a number of biochemically related acids. It appears possible that the mutant has a block in the tricarboxylic acid cycle, perhaps between oxaloacetate and malate or between oxalosuccinate and isocitrate. These mutants are particularly interesting since, if either of the presumed positions of the block are correct, the cyclical nature of the tricarboxylic acid cycle would be destroyed. It is more likely however that the block is elsewhere.

Further work on the sulfonamide-requiring mutant (*sfo*) discovered by Emerson (75) has reversed the previous interpretation. The evidence suggested that the sulfonamide did not act merely by displacing *p*-aminobenzoic acid from the site in which it is needed for normal functioning of the cell, but that the sulfonamide was itself needed in metabolism by the sulfonamide-requiring strain. Several mutant strains (*pab*) are known which require *p*-aminobenzoic acid for growth, and Zalokar (76) has shown that the double mutant *pab sfo* requires *p*-aminobenzoic acid for growth but that concentrations above  $2 \times 10^{-7}$  molar become increasingly toxic. It is presumed that *sfo* directs a reaction whereby *p*-aminobenzoic acid produces an inhibitory substance, the reaction requiring a somewhat higher concentration than is needed for normal growth. Emerson (77) was able to show that a sulfonamide-requiring strain heterocaryotic for *pab* would grow under conditions which would not permit appreciable growth of the pure strains.

Houlahan & Mitchell (78) have found that certain mutants ac-

accumulate inorganic phosphate, apparently a metaphosphate similar to, or identical with, that found in yeast and *Aspergillus niger*. It is possible that the accumulation results from unbalance due to the necessity of supplying a growth factor in the medium, for there is greater accumulation with a lower concentration of growth factor and in some cases accumulation depends upon the substance added, while accumulation may be prevented by the introduction of a second genetic block further along in the reaction series.

The growth of some *Neurospora* strains is inhibited by canavanine, while others are resistant (79, 80). The ability to grow with canavanine segregates as a single gene difference, although some segregations appear to be more complicated. Possibly the resistant, or tolerant, strains possess an enzyme which splits canavanine, so removing an inhibitory effect. Horowitz & Srb (79) find that *L*-arginine will completely reverse the inhibition, while *L*-lysine and methionine will do so partially.

Ryan (81) has introduced a new method for the assay of the growth of mutants. This involves the determination of the rate of germination of conidia by a rapid and elegant technique in which the proportion of conidia germinated is measured after fairly short intervals.

*Bacteria*.—The most notable advance in the past few years has been the demonstration that one strain, at least, of one species of bacterium and at least one species of bacteriophage, possesses a method of sexual reproduction that is analogous genetically to that occurring in other sexually reproducing organisms. The principle of the demonstration is very simple. It involves merely the proof that a mixture of two mutants *a* and *b* will generate the recombinants *a<sup>+</sup>b<sup>+</sup>* and *ab*. If the mutants were biochemically deficient ones, plating a mixture of them on minimal medium would allow only the prototrophic recombinants *a<sup>+</sup>b<sup>+</sup>* to grow. However, such prototrophs would also be derived by back mutation of either mutant and so be of purely vegetative origin. If the process of sexual reproduction is relatively a rare one, the experimental recognition of it becomes the troublesome one of attempting to show a greater frequency of prototrophs from mixtures of mutants than can be accounted for by reverse mutation. The misleading effects of reverse mutation can be virtually eliminated by using multiple mutants in the experiments so that a prototroph could be obtained vegetatively by reverse mutation only if two or three different

back mutations occurred simultaneously. This is the basis of the technique employed by Lederberg & Tatum [see (99)] in their demonstration that race K-12 of *E. coli* reproduces sexually, generating genetic recombinants. Inocula of distinct multiple mutants, each usually different from wild type by three biochemical deficiencies, were mixed in complete medium and incubated for one to two days. The cells were then washed thoroughly and plated into minimal agar petri plates, to which various supplements were added as required. Various recombinant types appeared, including both prototrophs and deficient types that had derived a deficiency from each parent. Thus a mixture of the two triply deficient mutant strains, requiring, respectively, threonine+leucine+thiamine and biotin+phenylalanine+cystine, gave in addition to prototrophic recombinants others which required, for examples, threonine+phenylalanine, biotin+leucine, biotin+threonine, and biotin+thiamine.

Lederberg (82) has been able to demonstrate that the recombination process is an orderly one. The formation of the complementary recombination types has been demonstrated by making use of characters other than the biochemical deficiencies used as a sieve to screen out all biochemical nonrecombinants. The particular characters employed were chiefly abilities to adapt to ferment specific sugars such as lactose and resistance (or sensitivity) to specific bacteriophages of the *T* group. In suitable reciprocal pairs of crosses in which resistance was in one strain in one cross and in the other strain in the other cross, an inequality of phage sensitive and phage resistant prototrophs is reversed in a way consistent with the particular phage gene being linked to one of the biochemical genes. Indeed by following the mutual relations of a number of characters, including the biochemical deficiencies, it emerges that all known *E. coli* genes are situated in one linkage group in which they display a linear order with respect to one another. The data agree with the behaviour predictable upon a hypothesis of a single linear chromosome bearing the genes in tandem and undergoing homologous segmental exchanges like crossing-over in higher organisms.

These observations have been confirmed by other workers, though only with the same strain of *E. coli*, and notably Haas, Wyss & Stone (83) have demonstrated an increase in the rate of recombination among the surviving cells after a small dose of ultra-

violet irradiation. The absolute numbers of recombinant prototrophs are not substantially greater than in the control series so that differential survival cannot be excluded.

Lederberg (84) has also found unstable prototrophs that appear to be segregating heterozygous diploids. The capacity to produce appreciable numbers of persistent heterozygous diploids is inherited. In the heterozygotes the wild type alleles of several fermentation and nutritional factors are dominant, as they are shown to be in *Neurospora* by heterocaryon test. Sensitivity to phage T1 is dominant to resistance to it.

Recognition of the genic basis of bacterial inheritance does not depend upon proof of a sexual phase in bacteria. But at once more powerful genetic methods become possible and the case for the similarity of the processes of mutation in bacteria and higher organisms is strengthened. It is particularly interesting to note in this connection that Lederberg (85) has found that different lactose nonfermenting mutants vary in their revertibility. Moreover, some reversions are due not to back mutation of the lactose gene itself, but of another which has the effect of suppressing the inactivity of the mutant lactose nonfermenter.

Improvements in the methods of measuring spontaneous mutation rates have been made (86, 87) and applied especially to a study of the mutation of *E. coli* strain B from sensitivity to resistance to specific members of the T group of bacteriophages. Some methods employ the rate of appearance of phenotypically resistant clones during bacterial multiplication, others the frequency of resistant individuals. The latter measures give values about six times greater than the former ones. This implies that when a clone first becomes resistant it usually contains more than one mutant individual, and therefore that the mutation in the clone occurred sometime prior to its becoming phenotypically detectable. In the case of mutation to resistance to T1 phage, Newcombe (87) shows that the lag between mutation and expression is about 2.6 generations. However, in the case of mutation to streptomycin resistance (88) there is no difference in the rates measured by the two groups of methods, thus showing that there is no appreciable phenotypic lag in this case and that streptomycin resistance may be dominant to susceptibility to the antibiotic. It is reasonable to expect that the occurrence of a lag between mutation and phenotypic expression would depend upon whether the character is associated with

the presence or the absence of a substance. If the latter, the expression of a mutant would require the decay or dilution of a previously existing substance. If the substance is relatively stable, a lag will occur and this is what appears to happen in the origin of phage resistance. If the substance is quite unstable, it is possible that there would be no detectable lag, subject to the cells being haploid and uninucleate.

Newcombe (89) has introduced a modification of the Luria-Delbrück fluctuation technique for the distinction of "adaptation" and "spontaneous mutation" hypotheses. It has the merit of being independent of any particular statistical argument and of being technically simpler to apply. It depends upon the same principle that if a character change is due to a spontaneous mutation, the individuals expressing it will tend to occur in clusters. Plate cultures are incubated for a few (three to six) hours and then alternate ones are spread with 0.1 ml. of sterile saline. All plates are then subjected to a treatment capable of disclosing resistant mutants; for example, the plates may be sprayed with a phage suspension. The plates, after incubation, show colonies, the numbers of which should show no striking differences between unspread and spread plates if adaptation is responsible, while the number of colonies on spread plates would be greater than on unspread plates if spontaneous mutation is responsible. In the case of mutation to resistance to T1 phage, the latter behaviour is found. Ryan (90, 91) has shown that the reversion to histidine independence of histidineless *E. coli* is not induced by absence of the growth factor, but occurs spontaneously during growth of the culture in its presence. The experiments on the reversion of histidineless (92) illustrate the necessity for strict purity of the media used, since small amounts of histidine allow the growth of microcolonies which give an appreciable frequency of reversion. Thus far, no case of specific induction has been observed. The streptomycin resistant and requiring mutants of *Meningococcus* (93) have not been tested critically, but Newcombe & Hawirko (88) show similar *E. coli* mutants are spontaneous and selected by the drug.

Stone, Wyss & Haas (94) showed that ultraviolet irradiation of the substrate led to greater numbers of mutants amongst *Staphylococcus* cells subsequently grown in it. The particular mutants observed were those exhibiting resistance to penicillin or to streptomycin. Tests proved that the amino acids were the sensitive

substances in the medium. It was later found (96) that hydrogen peroxide added to the medium also raises the mutation rate. Also, when individual substances, such as phenylalanine, tryptophane, tyrosine, adenine, uracil, and guanine, were treated with hydrogen peroxide and later added to the culture medium, the mutation rate was raised. Very sensitive chemical methods failed to show any residual hydrogen peroxide present in the treated medium at the time of inoculation. The suggestion is made that the mutagenic substances are organic peroxides and that these are produced by irradiation as well as by hydrogen peroxide. It has been demonstrated also that mutations can be induced in dry bacteria (98), so the formation of organic peroxides need not be an exclusive method. Convincing evidence has been obtained (95) that the irradiated substrate is not merely a selective one favouring pre-existing mutants. The growth of a culture in irradiated medium is dependent upon the size of the inoculum used (97), a small inoculum dying off rapidly after slight initial growth. Evidently an intracellular enzyme is responsible for protecting the large inocula. Indeed it was found that catalase treatment of irradiated or of peroxide-treated media completely removed the growth inhibitory and the mutagenic principles.

*Viruses.*—Some of the most remarkable work on the viruses has been the proof that some of them, particularly the T group of species that parasitize the B strain of *E. coli*, are fairly complex organisms each with a characteristic morphology and each containing a number of genetic units analogous to the genes of higher organisms. Moreover, as reported in a previous review (99), there is clear evidence of some kind of sexuality among bacteriophages whereby there is an orderly exchange of genetic units. Hershey & Rotman (100) have extended their work on T2 phage, particularly using genes controlling the inhibition of lysis. This phenomenon is a peculiar one, not properly understood, by which the lysate of wild type phage inhibits the lysis of infected bacteria suspended in it. Phage mutants (*r* types) occur which show no lysis inhibition. They can be identified also by their distinctive plaques, clear instead of with a mottled halo, when grown in plate culture. Two different mutants or one mutant and one wild type, for examples, can be mixedly infected into a single bacterium and yield progeny. A considerable number of *r* type mutants have been found and all so far tested proved to be genetically different. In mixed infections

of two *r*-types, a proportion of wild type and of double mutant type are produced, the proportions of the recombinant classes being equal. The experiments as a whole establish the multigenic nature of the phage and the existence of some sort of linkage system determining segregation and the reassortment of genes, but it is not certain that the system involves crossing-over between linear structures analogous to chromosomes.

The reactivation of phage particles inactivated by ultraviolet light (101) has been extensively studied by Luria & Dulbecco (102). Inactivated *coli*-phages are still adsorbed by sensitive bacteria. Bacteria infected by one inactive particle are not lysed and do not yield active phage. Where multiple infections of inactivated phage occur, a proportion of the infected bacteria are lysed and active phage is produced. It is assumed that inactivation is due to lethal mutations in a number of genetic units of the phage particle, and that production of active phage from inactive is due to recombination of non-lethal units to form active particles. In order to explain the very high frequency of recombination, the hypothesis is proposed that phage growth occurs by independent reproduction of each unit, followed by reassembly of the units into complete phage particles. This would mean that we have here a process of reproduction in which the units do not maintain their mutual relation during the process, unlike the genes constituting the chromosomes. Dulbecco (103) and Latarjet (104) have studied aspects of the intracellular growth of phage.

Dulbecco (105) reports that bacteriophage inactivated by ultraviolet may be photo-reactivated by strong visible light, the most effective wave lengths being short ones. Reactivation occurs only when the bacteria and phage are mixed before exposure to light. No reactivation of x-ray inactivated phage occurs.

Delbrück (106) describes biochemical mutants of T4 phage. They differ with respect to their requirements for co-factors of adsorption.

*Yeast*.—Winge & Roberts (107) have studied the inheritance of adaptive enzymes, distinguishing between genes determining fast and slow adaptation respectively. Their results are quite incompatible with the Lindegren cytogene theory, which has however been abandoned (11).

Ephrussi (1, 124 to 130) has shown that treatment of yeast with acriflavin leads to the development of strains characterised by slow

growth and a small final size of the colonies. The small strain is unable to utilise glucose by the oxidative pathway since it lacks cytochrome-oxidase and succinic dehydrogenase. Crossing with the normal, followed by isolation of the ascospores, leads to four haploid lines, each of normal type. The small strain itself is perfectly stable, never having reverted in more than 2000 cell generations. It is formed through mutation, or loss, of a cytoplasmic factor that like kappa in *Paramecium* cannot be replaced by the nuclear apparatus, though it may be dependent on the latter for its normal maintenance. The mutant appears to be a transformation analogous to the transformation of killer to sensitive *Paramecium* through loss of kappa particles from the cytoplasm.

*The killer character in Paramecium.*—Several papers have appeared which take the analysis of cytoplasmic inheritance in *Paramecium aurelia* substantially further; these include a symposium on plasmagenes, genes and characters (108). In a number of varieties, killer individuals produce an antibiotic substance, paramecin, that kills sensitive individuals. The killer character is dependent upon a cytoplasmic component, kappa, and a nuclear gene  $k^+$ . Kappa will multiply if  $k^+$  is present in the nuclei but as it cannot be initiated by this gene, some kappa must be present in the cytoplasm for more to be produced. If the allele  $k$  replaces  $k^+$ , kappa no longer multiplies. Individuals lacking kappa are sensitive to the paramecin irrespective of their nuclear genotype. Kappa is particulate and a strong killer contains many kappa particles. When the number of kappa particles in an animal is small it is a sensitive non-killer. Preer (109, 110) has given proof that a single particle is sufficient, if the animal grows slowly, to regenerate the killer character. The reduction in number of particles per animal is secured by growing the paramecia under conditions in which they are well fed and so multiply faster than the kappa particles they contain. A proportion of animals become completely depleted of kappa after a number of generations, and this allows computation of the original number of particles present. The mathematical treatment of the multiplication rate and chance distribution at fission of the animal has been considerably improved by methods developed by Otter [in (110)] and lead to revised estimates of the number of kappa particles in a strong killer as about 500, which is somewhat above the earlier estimates. Further, there is evidence of a logistic factor in that the rate of increase of kappa is greater when its concentra-

tion is lower. The rate of division of kappa increases with greater rate of division of the *Paramecium* up to a maximum. The kappa particles have an optimal temperature for maximum division rate, for example, stock G kappa has a maximal rate of 27°C., decreasing above and below this temperature and is inactivated above 30.4°C.

An independent estimate of number and of the size of the kappa particle has been obtained by an x-radiation method. Between 19,000 and 36,000 r units dose increasing proportions of killer animals become permanently sensitive and give only sensitive progeny. Above 36,000 r all animals and their progeny become sensitive. From the proportion of animals containing no kappa after different amounts of radiation, the number of surviving kappa particles may be calculated. By extrapolation the original number was determined as between 400 and 1600. The point on the dose-survival curve with the kappa concentration reduced to 37 per cent of the original gives the inactivation dose, about 3,500 r, and so an estimate of particle size. The size of kappa is appreciable, namely  $0.3\mu$  diameter or more. Subsequent to this result it was found (111) that the cytoplasm of most, if not all, killer stocks contain Feulgen positive particles, about 1000 to 2000 per cell and each 0.2 to  $0.5\mu$  diameter. Sensitives are free from them. Kappa is thus remarkably similar to a parasite or symbiont, for all of its characteristics could equally well characterize a rickettsia, a large virus, or a small bacterium. However, kappa has no harmful effects on its "host," indeed it actually protects it against the action of the paramycin produced. Its pathogenic action is limited to organisms it has not infected and to organisms in which it is in low concentration. At present, there is no compelling evidence for concluding either that kappa is a parasite or that it is not. The only feature that distinguishes it from other cytoplasmic elements is its possession of desoxyribonucleic acid.

Like other plasmagenes, such as the plastids of plants, kappa is able to undergo mutations. Dippell (112) has described various mutants in stock 51 of variety 4, which differ from the normal either in producing less paramycin or in having a different killing reaction, the sensitives spinning violently instead of blistering. It was proved that  $k^+$ , the nuclear gene required to maintain kappa, was unaltered. Some mutant killers contained two types of kappa, which could be separated by the usual depletion techniques. Ani-

mals with two types of kappa are protected from both paramacins whereas those with only one are sensitive to the other type of paramecin. The presence of two types of kappa in the same cell under the control of the same gene opens up the possibility for study of competition between cytoplasmic factors, and hence to an insight as to how diverse changes in cell functions and phenotypes may occur in the absence of genic change.

Austin (113) has shown that paramecin is itself particulate and that only a single particle is needed to kill a sensitive animal. The paramecin is produced as single discrete units at an average rate of one per killer in each five hour period in stock 51 of variety 4. It is of great interest that Van Wagtendonk (114, 115) has shown that the paramecin is a desoxyribonucleoprotein. It has a narrow pH stability range in the alkaline region, with a maximum at pH 8.5, but even here 7 per cent of its initial activity is lost after 30 min. at 30°C. The inactivation is monomolecular at all pH's. The heat of inactivation at pH 7 is 126,000 calories per mole, a value typical for enzymes and proteins, to either or both of which paramecin belongs. The inactivation is accelerated by proteinases such as pepsin and chymotrypsin. Desoxyribonuclease also inactivates it in the presence of magnesium or manganese, the action of magnesium being counteracted by citrate ions.

*Antigenic characters in Paramecium.*—In race 51 of variety 4, rabbit antisera have been obtained to four antigenic strains A, B, C, and D. Sonneborn and Lesuer (116) have shown that the inheritance of the antigenic types is cytoplasmically determined. There is no segregation of genic differences in respect to the antigens, so no genic differences exist or have so far been found. The antigenic traits of a strain can be permanently altered by exposure to dilute antiserum, sufficient to paralyse, followed by washing. This results in a considerable increase in the frequency of antigenically changed cultures. Thus the percentage of D type altered increases from zero to 100 per cent with increased exposure time and concentration of antibody. These changes appear to be directed mutations of cytoplasmic factors. A nonhomologous antiserum will paralyse an antigenic type concentration higher than that at which it will paralyse its homologous antigenic type. A given antiserum, therefore, contains all types of antibody, hence the corresponding antigenic type must have contained all types of antigen. The different antisera differ in the relative amounts of

the antibodies. This suggests that the antigens can be maintained in only one of a small number of stable proportions and that any conditions which greatly disturb the existing stable proportion may lead to establishment of a different stable proportion.

Subsequently, it was found that manipulation of environmental conditions such as temperature and food supply would induce these mass directed transformations in the absence of antisera (117, 118). Furthermore, evidence has been obtained that the production of antigens is under fairly direct genic control. Two stocks, numbers 51 and 29, of variety four are able to transform, respectively, to antigenic types A, B, C, D, E, G, and A, B, C, D, F, H. The capacity to transform to the type producing F antigen depends upon a gene present in stock 29 and lacking in stock 51. The difference between stocks 29 and 51 in antigenic potentialities is thus gene-determination, but the differences in antigenic type realised within either stock appears to be plasmagene-determined. The specific gene determines the capacity to produce and the capacity to maintain F antigen plasmagene. In the absence of the gene it is not initiated or, if already present, it does not reproduce. The different antigenic types within a stock appear to depend upon some type of mutual competition or of reciprocal inhibitions among the reactions which lead from genes to antigens, so that one antigen predominates. Clearly the fact remains that the hereditary differences between the antigenic types are determined by something residing in the cytoplasm, regardless of whether the plasmagene interpretation is confirmed by further work.

Many cases of changes of antigenic type and of changes of drug resistance in various organisms may be examples of similar mechanisms. *Dauermodifikationen*, the long-lasting but impermanent changes observed by Jollos and others, may be of similar type. Kimball (119, 120) has investigated another case, involving antigenic differences, in variety 1 of *Paramecium aurelia*.

Metz (121) has reported experiments on the nature and mode of action of the mating type substances in variety 4, in which the mating type is cytoplasmically determined but may change. This implies at least two cytoplasmic factors and that the agglutinative mating reaction results from the interaction of complementary mating type substances. Living animals are clumped by dead ones of the opposite sex, though not if the latter have been treated with antisera. The living animals then undergo autogamy. CM (cannot

mate) animals will initiate mating in the opposite sex, but are not further activated themselves. The CM block prevents activation proceeding in CM animals beyond the initial stage of clumping.

*Growth and differentiation.*—Ideas of tissue differentiation by the acquisition of different plasmagenes or enzyme patterns, or different balances of them, have received great support from the work on *Paramecium*. Billingham and Medawar (122) have continued their study of pigment spread and cell heredity in the guinea pig skin. Stormont (123) has shown that the J substance of bovine erythrocytes is acquired by the erythrocytes from the blood plasma. Twins may differ in respect to its presence or absence. The synthesis of the substance does not occur in the cells in which the factor is recognised.

## LITERATURE CITED

1. *Proc. Eighth Intern. Congr. Genetics*, 696 pp. (Bonnier, G., and Larsson, R., Eds., 1949)
- 2a. SONNEBORN, T. M., *Advances in Genetics*, **1**, 263-358 (1947)
- 2b. IRWIN, E. A., *Advances in Genetics*, **1**, 133-59 (1947)
- 3a. CASPARI, D., *Advances in Genetics*, **2**, 1-66 (1948)
- 3b. HESTON, W., *Advances in Genetics*, **2**, 99-125 (1948)
4. MULLER, H. J., LITTLE, C. C., AND SNYDER, L. H., *Genetics, Medicine and Man*, 158 pp. (Cornell Univ. Press, New York, 1947)
5. GRÜNEBERG, H., *Animal Genetics and Medicine*, 296 pp. (Hamish Hamilton Medical Books, London, 1947)
6. CREW, F. A. E., *Genetics in Relation to Clinical Medicine*, 111 pp. (Oliver & Boyd, Edinburgh, 1947)
7. *Genetics and Cancer: Symposium on the Genetics of Cancer*, *Brit. J. Cancer*, **2**, 87-176 (1949)
8. *Symposia Soc. Exptl. Biol., Growth*, **II**, 365 pp. (Danielli, J. F., and Brown, R., Eds., 1948)
9. MATHER, K., *Biometrical Genetics*, 162 pp. (Methuen, London, 1949)
10. DEMEREC, M., "Nucleic Acid," *Cold Spring Harbor Symposia Quant. Biol.*, **12**, 314 pp. (1948)
11. LINDEGREN, C. C., *The Yeast Cell, Its Genetics and Cytology*, 365 pp. (Educational Publishers, Inc., St. Louis, 1949)
12. LEDERBERG, J., *Heredity*, **2**, 145-98 (1948)
13. BURNET, F. M., AND FENNER, F., *Heredity*, **2**, 289-324 (1948)
14. L'HERITIER, P., *Heredity*, **2**, 325-48 (1948)
15. AUERBACH, C., *Biol. Revs. Cambridge Phil. Soc.*, **24**, 355-91 (1949)
16. DEMEREC, M., *Science*, **105**, 634 (1947)
17. LATARJET, R., *Compt. rend. soc. biol.*, **142**, 453 (1948)
18. WITKIN, E. M., *Cold Spring Harbor Symposia Quant. Biol.*, **12**, 256-69 (1948)
19. FRIES, N., AND KIHLMANN, B., *Nature*, **162**, 573-74 (1948)
20. LEVAN, A., AND HIN TJIO, J., *Hereditas*, **34**, 250-52, 453-84 (1948)

21. VOGT, M., *Experientia*, **4**, 68 (1948)
- 21a. OEHLKERS, F., in *Proc. Eighth Intern. Congr. Genetics*, 635-37 (1949)
22. KAPLAN, W. D., *Science*, **108**, 43 (1948)
23. D'AMATO, F., AND GUSTAFSSON, A., *Hereditas*, **34**, 181-92 (1948)
24. GUSTAFSSON, A., AND MACKEY, J., *Hereditas*, **34**, 371-86 (1948)
25. SWANSON, C. P., AND GOODGAL, S. H., *Genetics*, **33**, 127 (1948)
26. KAUFMANN, B. P., AND GAY, H., *Genetics*, **33**, 112 (1948)
27. DARLINGTON, C. D., AND KOLLER, P. C., *Heredity*, **1**, 187-222 (1947)
- 27a. FORD, C. E., *Proc. Eighth Intern. Congr. Genetics*, 570-71 (1949)
28. FRIES, N., *Nature*, **159**, 199 (1947)
29. LEIN, J., MITCHELL, H. K., AND HOULAHAN, M. B., *Proc. Natl. Acad. Sci. U. S.*, **34**, 435-42 (1948)
30. WESTERGAARD, M., AND MITCHELL, H. K., *Am. J. Botany*, **34**, 573-77 (1947)
31. EMERSON, M. R., *J. Bact.*, **55**, 327-30 (1948)
32. TATUM, E. L., BARRATT, R. W., AND CUTTER, V. M., *Am. J. Botany*, **35**, 803 (1948)
33. TATUM, E. L., BARRATT, R. W., AND CUTTER, V. M., *Science*, **109**, 509-11 (1949)
34. LEDERBERG, J., AND TATUM, E. L., *J. Biol. Chem.*, **165**, 381-82 (1946)
35. MEYERSBURG, R., POMPER, S., AND CUTTER, V. M., *Science*, **109**, 446-47 (1949)
36. PONTECORVO, G., *J. Gen. Microbiol.*, **3**, 122-26 (1949)
37. FRIES, N., *Hereditas*, **34**, 338-50 (1949)
38. FRIES, N., *Physiologia Plantarum*, **1**, 330-41 (1948)
39. DAVIS, B. D., *Arch. Biochem.*, **20**, 166-67 (1949)
40. DAVIS, B. D., *Proc. Natl. Acad. Sci. U. S.*, **35**, 1-10 (1949)
41. MITCHELL, H. K., AND LEIN, J., *J. Biol. Chem.*, **175**, 481-82 (1948)
42. MITCHELL, H. K., HOULAHAN, M. B., AND LEIN, J., *Genetics*, **33**, 620-21 (1948)
43. WAGNER, R. P., AND GUIRARD, B. M., *Proc. Natl. Acad. Sci. U. S.*, **34**, 398-402 (1948)
44. WAGNER, R. P., *Proc. Natl. Acad. Sci. U. S.*, **35**, 185-89 (1949)
45. HOROWITZ, N. H., *Genetics*, **33**, 612-13 (1948)
46. BONNER, D., *Science*, **108**, 735 (1948)
47. LEDERBERG, J., *Genetics*, **33**, 617 (1948)
48. LAUGHAN, J. R., *Genetics*, **33**, 488-517 (1948)
49. LAUGHAN, J. R., *Proc. Natl. Acad. Sci. U. S.*, **35**, 167-78 (1949)
- 49a. LINDEGREN, C. C., *Proc. Eighth Intern. Congr. Genetics*, 338-55 (1949)
50. LEWIS, D., *Heredity*, **2**, 219-36 (1948)
- 50a. LEWIS, D., *Proc. Eighth Intern. Congr. Genetics*, 618-19 (1949)
51. STADLER, L. J., AND ROMAN, H., *Genetics*, **33**, 273-303 (1948)
52. GILES, N. H., AND LEDERBERG, E. Z., *Am. J. Botany*, **35**, 150-57 (1948)
53. GILES, N. H., *Am. J. Botany*, **35**, 800-1 (1948)
54. GILES, N. H., *Genetics*, **33**, 105 (1948)
55. ZECHMEISTER, L., AND WENT, F. W., *Nature*, **162**, 847-48 (1948)
56. MACKINNEY, G., AND JENKINS, J. A., *Proc. Natl. Acad. Sci. U. S.*, **35**, 284-91 (1949)
57. KEITT, G. W., LEBEN, C., AND SHAY, J. R., *Am. J. Botany*, **35**, 334-36 (1948)

58. TATUM, E. L., AND BONNER, D., *J. Biol. Chem.*, **151**, 349 (1943)
59. MITCHELL, H. K., AND NYC, J. F., *Proc. Natl. Acad. Sci. U. S.*, **34**, 1-5 (1948)
60. BONNER, D., *Proc. Natl. Acad. Sci. U. S.*, **34**, 5-9 (1948)
61. TEAS, H. J., HOROWITZ, N. H., AND FLING, M., *J. Biol. Chem.*, **172**, 651-58 (1948)
62. HOROWITZ, N. H., *J. Biol. Chem.*, **171**, 255-64 (1947)
63. TEAS, H. J., *Genetics*, **33**, 632 (1948)
64. PHINNEY, B. O., *Genetics*, **33**, 624 (1948)
65. MITCHELL, H. K., AND HOULAHAN, M. B., *J. Biol. Chem.*, **174**, 883-87 (1947)
66. HOULAHAN, M. B., AND MITCHELL, H. K., *Proc. Natl. Acad. Sci. U. S.*, **34**, 465-70 (1948)
67. HOULAHAN, M. B., AND MITCHELL, H. K., *Proc. Natl. Acad. Sci. U. S.*, **33**, 223-29 (1947)
68. MITCHELL, H. K., AND HOULAHAN, M. B., *Federation Proc.*, **6**, 506-9 (1947)
69. MITCHELL, H. K., HOULAHAN, M. B., AND NYC, J. F., *J. Biol. Chem.*, **172**, 525-29 (1948)
70. LORING, H. S., AND FAIRLEY, J. L., *J. Biol. Chem.*, **172**, 843-44 (1948)
71. FAIRLEY, J. L., AND LORING, H. S., *J. Biol. Chem.*, **177**, 451-59 (1949)
72. PIERCE, J. G., AND LORING, H. S., *J. Biol. Chem.*, **176**, 1131-40 (1948)
73. FRIES, N., *Physiologia Plantarum*, **2**, 78-102 (1949)
74. LEWIS, R. W., *Am. J. Botany*, **35**, 292-95 (1948)
75. EMERSON, S., *J. Bact.*, **54**, 195-207 (1947)
76. ZALOKAR, M., *Proc. Natl. Acad. Sci. U. S.*, **34**, 32-36 (1948)
77. EMERSON, S., *Proc. Natl. Acad. Sci. U. S.*, **34**, 72-74 (1948)
78. HOULAHAN, M. B., AND MITCHELL, H. K., *Arch. Biochem.*, **19**, 257-64 (1948)
79. HOROWITZ, N. H., AND SRB, A. M., *J. Biol. Chem.*, **174**, 371-78 (1948)
80. TEAS, H. J., AND HOROWITZ, N. H., *Genetics*, **33**, 127-28 (1948)
81. RYAN, F. J., *Am. J. Botany*, **35**, 497-503 (1948)
82. LEDERBERG, J., *Genetics*, **32**, 505-25 (1947)
83. HAAS, F. O., WYSS, O., AND STONE, W. S., *Proc. Natl. Acad. Sci. U. S.*, **34**, 229-32 (1948)
84. LEDERBERG, J., *Proc. Natl. Acad. Sci. U. S.*, **35**, 178-84 (1949)
85. LEDERBERG, E., *Genetics*, **33**, 617 (1948)
86. BEALE, G. H., *J. Gen. Microbiol.*, **2**, 131-42 (1948)
87. NEWCOMBE, H. W., *Genetics*, **33**, 447-76 (1948)
88. NEWCOMBE, H. W., AND HAWIRKO, R., *J. Bact.*, **57**, 565-72 (1949)
89. NEWCOMBE, H. W., *Nature*, **164**, 150-51 (1949)
90. RYAN, F. J., *Proc. Natl. Acad. Sci. U. S.*, **34**, 425-35 (1948)
91. RYAN, F. J., AND SCHNEIDER, L. K., *J. Bact.*, **56**, 699-708 (1948)
92. RYAN, F. J., AND SCHNEIDER, L. K., *Genetics*, **34**, 72-91 (1949)
93. MILLER, C. P., AND BOHNHOFF, M., *J. Bact.*, **54**, 467-81 (1947)
94. STONE, W. S., WYSS, O., AND HASS, F., *Proc. Natl. Acad. Sci. U. S.*, **33**, 59-66 (1947)
95. STONE, W. S., HAAS, F., CLARK, J. B., AND WYSS, O., *Proc. Natl. Acad. Sci. U. S.*, **34**, 142-49 (1948)
96. WYSS, O., STONE, W. S., AND CLARK, J. B., *J. Bact.*, **54**, 767-72 (1947)
97. WYSS, O., CLARK, J. B., HAAS, F. O., AND STONE, W. S., *J. Bact.*, **56**, 51-57 (1948)

98. DEVI, P., PONTECORVO, G., AND HIGGINBOTTOM, C., *Nature*, **160**, 503-4 (1947)
99. BEADLE, G. W., *Ann. Rev. Physiol.*, **10**, 17-42 (1948)
100. HERSHEY, A. D., AND ROTMAN, R., *Proc. Natl. Acad. Sci. U. S.*, **34**, 89-96 (1948)
101. LURIA, S. E., *Proc. Natl. Acad. Sci. U. S.*, **33**, 253-64 (1947)
102. LURIA, S. E., AND DULBECCO, R., *Genetics*, **34**, 93-125 (1949)
103. DULBECCO, R., *Genetics*, **34**, 126-32 (1949)
104. LATARJET, R., *J. Gen. Physiol.*, **31**, 529-46 (1948)
105. DULBECCO, R., *Nature*, **163**, 949-50 (1949)
106. DELBRÜCK, M., *J. Bact.*, **56**, 1-16 (1948)
107. WINGE, O., AND ROBERTS, C., *Compt. rend. trav. lab. Carlsberg Sér. physiol.*, **24**, 263-315 (1948)
108. SONNEBORN, T. M., *Am. Naturalist*, **82**, 26-34 (1948)
109. PREER, J. R., *Am. Naturalist*, **82**, 35-42 (1948)
110. PREER, J. R., *Genetics*, **33**, 349-404 (1948)
111. PREER, J. R., *Genetics*, **33**, 625 (1948)
112. DIPPPELL, R. V., *Am. Naturalist*, **82**, 43-50 (1948)
113. AUSTIN, M. L., *Am. Naturalist*, **82**, 51-59 (1948)
114. VAN WAGTENDONK, W. J., *Am. Naturalist*, **82**, 60-68 (1948)
115. VAN WAGTENDONK, W. J., *J. Biol. Chem.*, **173**, 691-704 (1948)
116. SONNEBORN, T. M., AND LESUER, A., *Am. Naturalist*, **82**, 69-78 (1948)
117. SONNEBORN, T. M., *Proc. Natl. Acad. Sci. U. S.*, **34**, 413-18 (1948)
118. BEALE, G. H., *Proc. Natl. Acad. Sci. U. S.*, **34**, 418-23 (1948)
119. KIMBALL, R. F., *Genetics*, **32**, 486-99 (1947)
120. KIMBALL, R. F., *Am. Naturalist*, **82**, 79-84 (1948)
121. METZ, C. B., *Am. Naturalist*, **82**, 85-95 (1948)
122. BILLINGHAM, R. E., AND MEDAWAR, P. B., *Heredity*, **2**, 29-48 (1948)
123. STORMONT, C., *Proc. Natl. Acad. Sci. U. S.*, **35**, 232-37 (1949)
124. EPHRUSSI, B., *Proc. Eighth Intern. Congr. Genetics*, 566-67 (1949)
125. EPHRUSSI, B., HOTTINGUER, H., AND CHIMENES, A.-M., *Ann. inst. Pasteur*, **76**, 351-67 (1949)
126. EPHRUSSI, B., HOTTINGUER, H., AND TAVLITZKI, J., *Ann. inst. Pasteur*, **76**, 419-50 (1949)
127. TAVLITZKI, J., *Ann. inst. Pasteur*, **76**, 497-509 (1949)
128. SLONIMSKI, P. P., *Ann. inst. Pasteur*, **76**, 510-30 (1949)
129. SLONIMSKI, P. P., AND EPHRUSSI, B., *Ann. inst. Pasteur*, **77**, 47-63 (1949)
130. EPHRUSSI, B., L'HÉRITIER, P. L., AND HOTTINGUER, H., *Ann. inst. Pasteur*, **77**, 64-83 (1949)

## GROWTH<sup>1</sup>

BY PAUL C. ZAMECNIK AND JOSEPH C. AUB

*The Medical Laboratories of the Collis P. Huntington Memorial Hospital  
of Harvard University, at the Massachusetts General Hospital,  
Boston, Massachusetts*

The end of World War II marks a convenient dividing line between old and new approaches to the problem of defining the mechanisms involved in the growth of living organisms. The post-war era has been marked by the appearance of radioactive isotopes, chromatography, genetic mutants of unicellular organisms, and metabolic analogues as tools with which the phenomena of growth are being explored. The Committee on Growth of the National Research Council, acting on behalf of the American Cancer Society, has provided valuable financial support in this field, which is reflected in a growth in the number of workers applying energy toward a solution of this problem. Since the literature bearing on growth during this period is too voluminous to record, the present review, as seen through medically-trained eyes, will be concerned only with that portion of the field which bears on protein metabolism, and which was published in the available journals from January, 1948 to July, 1949.

Several excellent collections of papers reviewing the problems of growth from a variety of points of view have appeared during the past year, providing coverage up to the middle of 1947 (1 to 4). In addition, in 1948, Koser (5) reviewed the subject of growth factors for microorganisms, Gale (6) discussed synthesis of bacterial protoplasm, and Cannon (7) published a short monograph on "Some Pathogenic Consequences of Protein and Amino Acid Deficiencies" in higher animals.

In general, the focus, in dealing with problems of growth, has shifted from a concern with the increase in numbers and weights of cells to a characterization of the machinery involved in the growth process in the growing cell. It would appear best, therefore, to complement one aspect of these reviews by concentrating on studies bearing on growth and protein metabolism which have appeared since the above-mentioned reviews. In limiting this re-

<sup>1</sup> This is publication No. 677 of the Harvard Cancer Commission. The preparation of this review was aided by grants from the American Cancer Society.

view to one subject, it would also be desirable to limit it to one type of animal. This, however, is not possible because such varied species have been used. It must be borne in mind that the metabolic patterns of different species are not necessarily the same.

The following review can be divided into sections, discussing: newer methods used in studies on protein metabolism, experiments aimed at increasing our understanding of the mechanism of peptide and protein synthesis and degradation, studies on amino acid interconversions, amino acid transport across the cell membrane, amino acid requirements and the animal protein factor, amino acid antagonists and peptide-like growth inhibitors, tissue culture studies; hormonal relationships, and neoplasia as related to protein metabolism.

#### NEWER METHODS EMPLOYED IN STUDY OF PROTEIN METABOLISM

An elegant starch column chromatographic method for separation of amino acids has been devised by Moore & Stein (8 to 12). This is a quantitative extension of the pioneer chromatographic separation methods of Gordon, Martin & Synge (13, 14) and of Elsdon & Synge (15). Borsook *et al.* (16) report the isolation by means of starch column chromatography of a peptide from guinea pig liver homogenate in which  $C^{14}$ -labeled leucine turnover is 40 per cent when leucine is incubated for 6 hr. with the homogenate. Frantz *et al.* (17) have used the starch column to separate glycylglycine from glycine in their studies on the equilibrium of the glycine-glycylglycine reaction in the presence of a liver peptidase. Daly & Mirsky (18) have obtained a clear-cut separation of purines and pyrimidines using the starch column. It is apparent that starch column chromatography with automatic fraction collecting is a powerful addition to the radioactive isotope technique for studies of incorporation of amino acids into proteins and of interconversions of amino acids. That ion exchange resins may be similarly used for quantitative separations by adsorption-elution methods has been demonstrated by Cohn (19) and by Stein & Moore (20). For separation of closely related peptides such as those found in the new antibiotic bacitracin, however, counter-current distribution (21) appears to be more effective than starch column chromatography since the movement of long chain peptides on starch columns has thus far been found to be slow.

More widely used than the above methods have been the simpler, but less quantitative procedures for separation of amino acids, based on paper strip chromatography, as employed by Dent *et al.* (22), Roberts & Tishkoff (23), Haugaard & Kroner (24), Awapara (25) and others [as cited in a recent review (26)]. The paper strip chromatographic method allows a much more rapid exploration of the problems of amino acid separation, and the starch column method may be considered its quantitative complement rather than a competitor. Randall & Martin (27) mention a simple ancillary apparatus for collecting fractions from the starch column.

There is, of course, no way of distinguishing isomers of a given amino acid by the above methods. Darmon, Sutherland & Tristram (28) describe a new approach to this problem by means of infra-red analysis. They point out that this method of distinguishing isomers in protein hydrolysates (in this case D and L leucine) requires a large amount of material (5 to 10 mg.) as compared with microbiological assay, but possesses the advantage that a highly characteristic physical property of the molecule (its vibration frequency) is being used. Microbiological assay continues to give valuable information on the amino acid composition of proteins (29, 30, 31). For the uninitiated, Bonner's review (32) provides a concise exposition of the use of *Neurospora* in clarifying the relationship of genes to biochemical reactions. In a review on the kinetics of growth of microorganisms, van Niel (33) has pointed out the usefulness of the newer methodology of determining population densities by turbidity measurements with the aid of photoelectric apparatus in analyzing bacterial growth curves.

#### STUDIES ON PEPTIDE AND PROTEIN SYNTHESIS

A key piece of the problem-complex of growth is the mechanism of protein synthesis. Studies focused on this critical question are thus one of the spearheads of attack on the problems of growth. The increasing availability of stable and radioactive isotopes and of well engineered counting devices has resulted in initiation, in a number of laboratories, of a variety of interesting studies designed to shed light on the mechanism of protein synthesis (34 to 40). It was demonstrated that labeled amino acids, on incubation with surviving tissue slices in the presence of oxygen (39), became closely associated with the protein fractions of the slice. While it

appeared most likely that the labeled amino acids were being built into the peptide chains of cell proteins, the possibility of adsorption or combination of the amino acids with proteins in linkages other than in the true peptide bond remained. The term "incorporation" has been generally adopted in describing the results of such experiments in order to encompass this uncertainty.

It has been pointed out recently by Anfinsen *et al.* (41) that the same reservation about the demonstration of true protein synthesis may be applied to a large share of the *in vivo* experiments on which our concept of the dynamic state of protein metabolism is based. It is fair to say, however, that the greater the percentage of labeled amino acid incorporated into proteins during an experiment, the less is the likelihood that processes other than true peptide linkages can provide the total explanation. Thus, *in vivo* experiments are in general on firmer ground in this respect than slice experiments, and slice experiments, in turn, are on firmer ground than homogenate experiments.

Since the next logical step in clarifying the mechanism of incorporation of labeled amino acids into proteins was to use a more homogeneous preparation than the tissue slice, the tissue homogenate has been employed for this purpose. Tolbert (42), and Winnick *et al.* (43) have reported the utilization of  $C^{14}$ -labeled glycine in the process of amino acid incorporation by the protein of liver homogenate. The latter group points out (44) that a large portion of the  $C^{14}$  is contained in serine, as a result of conversion of glycine to serine. Borsook *et al.* (45) have made a similar study on the incorporation of labeled lysine into the proteins of guinea pig liver homogenate. They described two sets of conditions in which  $C^{14}$ -epsilon labeled lysine is incorporated. In the one case the enzyme system was the whole homogenate; in the other case, the system used was the precipitate obtained by centrifugation of 15-fold diluted homogenate at  $2,500\times g$ . Perhaps the most significant point in this report is the caution against generalizing from the findings on labeled lysine to the incorporation of other amino acids into proteins. They state that leucine and glycine, under the best conditions found so far for lysine, are incorporated far more slowly than lysine into homogenate protein. In view of the complexity of the systems involved and of the dangers of coprecipitation of amino acids and peptides with proteins (46), it is clear that interpretation of results dealing with incorporation of

amino acids into proteins of homogenate still presents difficulties.

Such considerations have led to a search for simpler systems than whole protein molecules with which to study the mechanism of formation of the peptide bond. Friedberg *et al.* (47) demonstrated the formation of a  $C^{14}$ -labeled dipeptide, leucylglycine, following the administration of carboxyl-labeled radioactive glycine and ordinary L-leucine to whole rats. By the injection of leucylglycine prior to sacrifice of the animals and of additional carrier later, the labeled dipeptide was isolated from tissue extracts. In homogenate experiments on liver, Borsook *et al.* (48) report the isolation of a peptide fraction in which labeled lysine is rapidly incorporated. The clearest results on true peptide bond synthesis thus far, however, have been obtained by Bloch (49), who demonstrated the synthesis of labeled glutathione. Incubation of liver homogenates in the presence of  $C^{14}$ -glycine or  $N^{15}$ -glutamic acid resulted in the formation of the labeled tripeptide. Adenosinetriphosphate (ATP) markedly accelerated the aerobic synthesis of glutathione. The possibility that phosphate bond energy plays a role in sparking the formation of the peptide bond (50, 51) thus moves a step closer to certainty. The work of Speck (52) provides collateral confirmation of this point of view. Using a purified extract of acetone dried pigeon liver, he finds that the enzymatic synthesis of the peptide bond in glutamine requires ATP. It has been suggested for many years that acetyl amino acids may possibly serve as activated intermediates in peptide bond synthesis. Using pigeon liver homogenates, however, Bloch (49) found no evidence for this view, nor did Simmonds *et al.* (53) in their studies on the utilization of leucine derivatives by a mutant strain of *Escherichia coli* which required an exogenous source of L-leucine for growth.

It appears unlikely that reversal of proteolysis can explain a net protein synthesis. Frantz *et al.* (17) have found that the equilibrium position in the reaction  $\text{glycylglycine} \rightleftharpoons \text{glycine}$  in the presence of a liver peptidase is 99.7 per cent toward hydrolysis, even with glycine present in a concentration of 1 *M*. That the proteolytic enzymes and peptidases may be involved in the "retailoring" of peptide chains once formed, however, is suggested by experiments of Simmonds & Fruton (54) and of Zamecnik & Frantz (55). Such a possibility would be analogous to the findings of Axelrod (56, 57) that in the presence of phosphatase, phosphate

in ester linkage may be transferred from one alcohol to another without passing through the inorganic state.

In the preceding discussion, little mention has been made of the use of labeled amino acids in metabolic studies on whole animals. In an interesting collaboration of a biochemical team and a medical team, London *et al.* (58), using  $N^{15}$ -labeled glycine, report a study of heme synthesis and red blood cell dynamics in normal humans and in subjects with polycythemia vera, sickle-cell anemia, and pernicious anemia. In the polycythemia vera they found a rate of erythrocyte and hemoglobin production approximately 2.5 times normal. In the sickle-cell anemia, the erythrocytes were destroyed indiscriminately rather than as a function of age. In the pernicious anemia there was both deficient formation and an increased rate of destruction of erythrocytes, as indicated by the studies on glycine-labeled heme and protoporphyrin.

An investigation along similar lines was reported by Grinstein *et al.* (59), who studied a case of "light sensitive" (congenital) porphyria, in which the hemoglobin and porphyrin metabolism were followed by means of  $N^{15}$ -labeled glycine. The uptake of the  $N^{15}$  by the hemoglobin protoporphyrin was considerably greater than that previously recorded for a normal subject.

Other studies, carried out on animals other than humans, give further information on the process of porphyrin and heme synthesis. Wittenberg & Shemin (60, 61) found that glycine is utilized for the formation of all four pyrrole rings of porphyrin, and Altman *et al.* (62) reported that heme could be synthesized in rabbit bone marrow homogenates, in experiments based on the use of labeled glycine. That glycine participates in many interesting and previously unsuspected synthetic reactions has recently been pointed out by Rittenberg (63).

The above studies all relate to synthetic reactions and efforts to define the mechanisms of protein synthesis. Less attention has been directed to the use of isotopes in the study of protein degradation in tissues. One such investigation was carried out by Schubert & Armstrong (64). Following injections of  $C^{14}$ -labeled sodium carbonate, they measured the "biological half life" of proteins in mature and growing rats. An interesting feature of their findings was the lack of turnover of  $C^{14}$  in the brain protein of young animals following its incorporation. The statement is made that the specific activity of  $C^{14}$  in the tissues and tissue com-

ponents of the growing rats greatly exceeded that of the mature animals. Since, however, the same dosage of radioactivity was administered to each set of rats, and since the mature rats weighed eight to ten times as much as the growing rats, it is to be expected that the concentration of radioactivity would be higher in the latter group, purely on the basis of the dosage given. In a review on nucleoproteins and protein synthesis, Caspersson (65) fortifies with new evidence his earlier point of view that nucleic acids and nucleoproteins play a vital role in the process of protein synthesis.

#### AMINO ACID SYNTHESIS AND INTERCONVERSIONS

In the autotrophic and chemotrophic organisms, the cell possesses the capacity to synthesize all the amino acids necessary for construction of protein (66, 67), and advantage can be taken of this capacity to obtain, by biological synthesis, labeled amino acids not otherwise available. In higher animals, fragments of this ability remain, but the details of the interconversions are only incompletely worked out. The interconvertibility of glycine and serine has been described by several workers (44, 68, 69) and a formate-like compound has been found to play a role in the condensation of glycine to form serine. Lichstein (70) has found biotin to be involved in the enzymatic decarboxylation and deamination of aspartic acid. Cohen & Grisolia (71) have continued their studies on the urea cycle, with the interesting finding that glutamic acid acts as the initial acceptor of carbon dioxide in the conversion of ornithine to citrulline. It appears that carbamylglutamic acid serves as the donor of the carbon dioxide to ornithine in this initial step in the urea cycle. Ratner & Pappas (72) have presented a beautiful, well-documented scheme for the physiological pathway of amino nitrogen transfer from amino acids to form urea, showing the interrelationships with the tricarboxylic cycle and with transamination. Thus the relations of carbohydrate and amino acid metabolism become even more closely knit. Krebs (73) began a search for reactions, other than urea synthesis, causing a disappearance of added ammonia in isolated liver preparations. The main reaction responsible for the removal of ammonia was found to be glutamic acid synthesis. Miller & Bale (74, 75) have shown that the carbon chain of  $C^{14}$ -labeled lysine may be transferred in part to arginine, aspartic, and glutamic acids, thus giving added evidence to that of Borsook *et al.* (76, 77)

that lysine is more active metabolically than was generally supposed. The use of *Neurospora* continues to uncover new interrelationships between amino acids, and to provide clues as to the minimum number of enzymes involved in the amino acid biosyntheses (32, 78).

#### AMINO ACID TRANSPORT ACROSS THE CELL MEMBRANE

In the progression of biochemical evolution from the unicellular autotrophic organisms up to the more complex multicellular forms, there is a loss of ability to synthesize amino acids and a correspondingly increased dependence on the environment to furnish certain of these indispensable growth units. It thus becomes possible to limit or to regulate the growth of such an amino-acid-dependent organism by interfering with the transport of the essential amino acid (or other essential metabolite) across the cell membrane. The pioneer studies of Gale & Taylor (79) and Gale & Rodwell (80) suggest that penicillin inhibits the growth of certain microorganisms which require added glutamic acid by preventing the accumulation of glutamic acid across the cell membrane. It is further stated that as certain staphylococcal strains become increasingly resistant to penicillin, they become correspondingly independent of an external supply of the amino acids required by the present strain. Christensen *et al.* (81, 82, 83) have made comparisons in the rat of the amino acid concentrations in extracellular and intracellular fluids, and have found them to be consistently higher in the latter. They have found the intracellular amino acid concentrations to be particularly high in fetal guinea pig tissues and associate the rapid growth of the fetal tissue with this finding. They have thus been led to postulate the presence of an active amino acid concentrating mechanism in the cell membrane. Christensen admits the possibility that the intracellular amino acids may be present in a labile bound form not distinguishable from free amino acid by the analytical methods employed. A high plasma level of one amino acid was observed to interfere with the concentration of other amino acids across the cell membrane. This finding did not, however, apply to high plasma levels of glutamic acid, which contributed in some way to the concentrating mechanism. Christensen further reports (84) that pyruvate is important in maintaining the "concentrating ability" of surviving slices of rat diaphragm. In this connection, the observations of

Krebs & Eggleston (85), that L-glutamate prevented the loss of potassium ions from slices of brain tissue suspended in a glucose-saline medium, are of interest. It thus appears that new factors are being uncovered which influence the active transport mechanisms of the cell membrane, and which could conceivably serve as control mechanisms on growth by regulating the supply of amino acids to the cells and its internal environment.

By a filter paper chromatographic technique, Awapara *et al.* (86, 87) have investigated the ability of kidney, liver, and muscle to concentrate amino acids injected intravenously into the rat. A pattern of concentration was found to be characteristic of each organ. Interconversions of amino acids were thought to be demonstrated in some cases, although the evidence is indirect.

A number of studies on the distribution of labeled amino acids in normal tissues have been made (88 to 91). The highest levels of radioactivity are in general found in two types of tissues: (a) those with high metabolic and mitotic rates, such as intestinal mucosa, bone marrow, and lymph nodes, and (b) those which manufacture proteins for secretion and distribution elsewhere, such as liver and pancreas.

#### AMINO ACID REQUIREMENTS AND THE ANIMAL PROTEIN FACTOR

A relatively recent development in nutritional assay studies is the use of a variety of test organisms including bacteria (92, 93), protozoa (94, 95), and insects (96, 97, 98) for exploration of nutritional requirements. In the more commonly used animal species, investigators have recently added stresses such as repeated pregnancies, thyroid feeding, and antimetabolites to bring out deficiency states not otherwise appreciable [cf. (99)]. Both of these trends imply that most of the deficiencies detectable by classical methods of study have been recognized.

At the time when Rose (100) reviewed his important findings on the nutritive significance of amino acids, the weanling rat was the standard test object for dietary studies on animals. Yardsticks of growth for rats have changed somewhat since, and in a more recent publication, Rose *et al.* (101) make the following statement: "Experiments have been conducted upon a relatively large number of young rats to determine the comparative efficacy for growth purposes of mixtures of 10 and 19 amino acids. Con-

trary to our observations of more than a decade ago, involving the use of a less satisfactory basal ration, the results demonstrate that the simpler mixture possesses a lower nutritive value as measured by the relative gains in weight of the subjects." Thus the animals which received the 10 essentials only, in an otherwise normal diet, gained only 70 to 75 per cent as much weight as littermates which consumed 19 amino acids. Addition of glutamine to a ration containing the 10 essentials (lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine, and arginine) resulted in a significant stimulating effect upon the rate of gain in weight. It is rather suddenly becoming apparent from a number of divergent points of view [cf. Krebs (102), Gale (79), Ratner (72), Cohen (71), Anfinsen (36), McIlwain (103, 104), and Christensen (83)], that glutamic acid occupies an unusually prominent position among amino acids in regulating the metabolic machinery of growing cells. Rittenberg (63) has pointed out the manifold conversion pathways open to the amino acid glycine. There appears to be good reason to look for other amino acids to play multiple roles in the cell economy.

With respect to the interpretation of growth curves in rats based on weight gain, Mayer (105) makes the pertinent comment that an increase in weight of a young rat by 5 gm. represents approximately 1 gm. of protein and 3 gm. of water, or an energy content of 4 to 5 calories; the same weight increase in an older animal represents 5 gm. of fat or 45 to 50 calories. This consideration must be taken into account in the establishment of growth equations.

In a review on optimal growth of the rat, Dunn *et al.* (106) point out that the types and proportions of substances which are near optimal for the growth of body components and for reproduction are well-known, but that little information is available on the efficacy of such diets in promoting longevity, physiological well-being, and resistance to disease. The work of Cannon (107, 108) bears importantly on this little understood relationship of dietary protein to the rate of antibody protein synthesis. In his opinion, dietary protein constitutes a major immunological contribution to antimicrobial defense whenever there is severe tissue protein deficiency and a concomitant impairment of the mechanisms of immunity. Cannon (7) has also found that a balanced amino acid mixture must be fed at one time if its optimal growth stimulation is expected. If the diet is deficient in a single amino acid, and if

that essential is fed separately several hours later, the effect of a complete diet is not obtained. This finding would appear to have practical implications in the human.

Pearce *et al.* (109) observed that mice fed diets deficient in tryptophane or methionine excreted abnormally high amounts of the ingested amino acids in the urine. Similar findings occurred on thiamine deficient diets (110).

The question as to whether preformed peptides may serve as accessory growth stimulants in diets containing amino acids as the source of protein building material is beginning to receive attention. It is quite likely that much variability will be found in this respect among growing organisms. Simmonds & Fruton (54) for example, isolated from a solution of L-leucylglycine a microorganism which grew in the presence of the dipeptide but not in a mixture of L-leucine and glycine. Maddy & Elvehjem (111), on the other hand, made a comparison of the growth of mice fed casein with that of mice fed rations in which free amino acids were the only source of nitrogen. They found the latter to supplement growth to a degree closely approaching that obtained with casein, or other intact proteins rich in the peptide-like growth factor streptogenin.

At this point, the very interesting and rapidly moving subject of the "animal protein factor" should be mentioned. Associated with animal protein materials have been found several factors (not protein in nature) not present in yeast or the major seed protein concentrates, which may be essential for growth and reproduction of such widely different species as mice, chickens, rats, *Tetrahymena*, and *Euglena* (98). Various relationships in this new field are discussed in detail in *Nutrition Reviews* (112 to 118). Only the experiments of Bosshardt *et al.* (119) will be mentioned here. These investigators subjected female mice to four successive pregnancies on a diet composed of 10 per cent wheat germ middlings, 40 per cent well-heated soy flour, 18 per cent hydrogenated cottonseed oil, 3 per cent cod liver oil, 7 per cent dried yeast, 18 per cent glucose, and 4 per cent salt mixture. All mice born in the fourth pregnancy died within three days after parturition. The young males from the first litters of the depleted females grew optimally if liver extract was added to the diet. A second method of depletion was also devised in which 0.5 per cent of iodinated casein possessing thyroid activity was added to the basal

diet. A retardation of growth resulted, which could be counteracted by liver extract. The relationship of this growth factor to vitamins B<sub>12</sub> and B<sub>14</sub> remains to be worked out.

#### AMINO ACID ANTAGONISTS AND PEPTIDE-LIKE GROWTH INHIBITORS

There are at least a half dozen ways in which interference with amino acid metabolism may retard growth. There may be (a) a hereditary inability to synthesize an essential amino acid, such as occurs in *Neurospora* mutants (120), (b) a hereditary impairment in the ability to utilize an amino acid, as in Fanconi's syndrome (121), (c) a deficiency in dietary intake of an amino acid, (d) an interference with its passage across the cell membrane (e) competition with a structurally related analogue at the site of combination with a synthetic enzyme (92, 122), and (f) depletion of the concentration available for protein synthesis by participation of the amino acid in other reactions such as conjugation (e.g., glycine  $\rightarrow$  hippuric acid) or enzymatic degradation. The experiments of Christensen *et al.* (81 to 84) on what may be termed cell membrane "transport competition" among amino acids have been mentioned. Whether this mechanism can explain the findings of Brickson *et al.* (123) that the balance of concentrations of leucine, isoleucine, valine, and methionine in the medium is important in the growth of lactic acid bacteria remains to be determined. Shive and colleagues (124, 125) have introduced the term "inhibition analysis" to describe their efforts to classify the various ways in which substances may reverse the growth-inhibiting effect of a given antimetabolite. Substances other than the essential metabolite itself may prevent the toxicity of the metabolic analogue. Such substances may be (a) precursors of the metabolite, (b) the product of the enzymatic reaction "blocked" by the analogue, and (c) substances exerting a "sparing action" on the product of this enzymatic reaction. Hitchings *et al.* (126) point out certain dangers in interpretation of data in inhibition analysis.

Use of the unnatural or D-isomer of an amino acid may or may not have a growth inhibitory effect (127, 128), depending on the ability of the organism involved to effect a conversion to the natural isomer.

There is, of course, abundant evidence of growth inhibition

produced in microorganisms by the addition to the medium of compounds structurally related to amino acids (129), since this line of approach is being exploited in an effort to uncover new antibiotics. Roper & McIlwain (104) have prepared a number of substances structurally related to glutamic acid, including the hydrazide, its acetone derivative, its benzaldehyde derivative, the hydroxamic acid, and an analogous sulfoxide and sulphone. With the exception of the benzaldehyde derivative and the sulphone, these compounds inhibited streptococcal growth. The basis of action is considered to be related to the metabolism of glutamine or glutamic acid. Borek & Waelsch (130) have also synthesized glutamic acid antimetabolites.  $\beta$ -Hydroxyglutamic acid and sulfoxide derived from methionine were found to be effective antimetabolites against glutamic acid in the metabolism of *Lactobacillus arabinosus*, probably by blocking the amidation of the amino acid to glutamine. Their growth inhibitory effect could be overcome by addition of glutamic acid or glutamine to the medium. These authors point out that such studies of antimetabolites on intact organisms cannot determine whether the antimetabolite acts by interfering with an enzyme reaction within the cell or by blocking the penetration of the metabolite. Ferger & du Vigneaud (131) have in a similar vein found that  $\beta$ -2-thienyl-L-alanine causes growth inhibition of *E. coli* and certain other microorganisms by interfering with the metabolism of phenylalanine.

It would be reasonable to expect that a search for competitive inhibitors would occasionally turn up a structural relative which might effectively substitute for the original metabolite. In such a search, Frieden & Winzler (132) discovered that a glycine homologue of thyroxine, a benzoic acid analogue of thyroxine, *N*-acetylthyroxine, and 3-5-diiodo-L-tyrosine had demonstrable thyroxine-like activity on amphibian metamorphosis and in prevention of increase in the thyroid gland weights of thiouracil-fed rats.

Little definite can be said about the biochemical site of the growth inhibition produced by a number of the better known antibiotics. Craig and colleagues have, however, found that gramicidin (133) and bacitracin (21) each consists of families of closely related peptides, and the unnatural configuration of part of the amino acid structure of gramicidin is well known. The structure of lycomarasmin, the tomato wilting toxin, is also suggestive of an

altered peptide (134, 135). It is, therefore, permissible to wonder whether such "screwty peptides" may not act by interfering with the normal process of protein synthesis within the cell.

#### TISSUE CULTURE STUDIES AND GROWTH

After many years of cultivation as a separate field of its own, the tissue culture technique has recently begun to move toward the foreground in nutritional research. It may not be rash to predict that in the next decade findings of great importance to nutrition and the knowledge of human disease will come from a study of growth factors on isolated pure strains of cells of different types. In order to use tissue cultures as effective test material, it is desirable to employ synthetic media, or a standardized medium containing protein. White (136) and Fischer (137) have both devoted recent effort to this problem of providing a well standardized basal cell diet on which to build nutritional studies. Fischer's experiments are particularly notable in providing a technique for evaluating the importance of each of the amino acids in the nutrition of myoblasts obtained from a chick embryo. He dialyzed chicken plasma and embryo juice and added them to a basic nutrient medium consisting of salts, amino acids, and vitamins. Thus, the plasma provided the clot necessary for cell growth but did not contribute amino acids or other dialyzable nutrients. In the first experiment it was determined that in the absence of amino acids in the basic nutrient, the cells died and disintegrated rapidly. The effect of omission of single amino acids was next studied. The absence of cystine resulted in complete failure of the culture to grow. Cystine could be replaced by glutathione but not by methionine. Omission of glutamic acid caused only a slight retardation of growth. If the glutamic acid was replaced by glutamine, the rate of growth increased enormously. The absence of lysine from the growth medium surprisingly enough had only a slight effect or none at all on the growth of the myoblasts. Osteoblasts were, however, more sensitive to lysine deficiency. These and findings of Fischer on other amino acids imply that the amino acid requirements of a single tissue may differ from those of an entire animal. The liver may serve as the synthetic factory for a so-called dispensable amino acid, which may then be distributed to the other tissues. The amino acid requirements of an isolated tissue may, however, be found to be more stringent than those of the animal as a whole.

Earle and colleagues (138) have achieved the remarkable feat of growing cultures of cells from a single cell. The concept which led to this success was that "the single cell fails to grow because even our best culture media are so inadequate as to need extensive modification by the cells before utilization." These investigators, therefore, reduced the amount of culture medium bathing the single cell, and supplied the cell with a culture medium already adjusted by the growth of large cultures of living cells, and obtained extensive growth and subcultures, starting with a single cell.

Gey *et al.* (139) found that reduction of temperature, prolongation of intervals between renewals of the nutrient medium, and reduction in concentration of some of the nutrients in roller tube tissue cultures resulted in maintenance of the cultures with little attention over long periods of time at low metabolic rates. The possibility is suggested that such cultures may serve as a baseline against which the effect of specific supplements can be measured.

The possibility of growing explants of human embryo endocrine organs, and using them as a source of supply for transplantation into endocrine deficient humans has been tried, with some success, by Gaillard (140). He reports a few cases of apparently successful transplantation of parathyroid gland explants into hypoparathyroid humans. He states that former failures may have been due to differentiation of culture tissues by prolonged growth in a medium from young embryos. By growing his parathyroid explants in a "dynamic medium," consisting of additions of press juice from progressively older embryos, he avoided this dedifferentiation of the parathyroid gland structure.

Brues & Naranjo (141) describe an ingenious arrangement for measuring uptake of  $C^{14}$  from bicarbonate by tissue cultures of chick embryo muscle. Cultivation of the tissue was carried out in a specially constructed bottle with a nylon window through which  $C^{14}$  activity of the tissue could be measured. Such arrangements offer the possibility of studying the rate of incorporation of  $C^{14}$ -labeled metabolites into rapidly growing tissue as contrasted with the less physiological surviving slice technique currently employed (142) in such studies.

#### HORMONAL RELATIONSHIPS TO PROTEIN METABOLISM

The past year has witnessed at least one major event in this field: the crystallization of the anterior pituitary growth hormone

by Li, Evans & Simpson (143). The point of view has also grown that the time is ripe to look for the effect of purified hormones on enzyme systems, an idea which received impetus from studies of Cori and colleagues (144) on the effect of insulin on the hexokinase system.

To the biochemical isolation studies of Li *et al.* (145, 146) has been added the highly useful large scale fractionation procedure of Wilhelmi *et al.* (147), which has made possible the crystallization of anterior pituitary growth hormone on a commercial level. This method depends on the fractionation with ethanol at low temperatures (after the methods devised by Cohn and associates) of a calcium hydroxide extract of ground, fresh bovine anterior pituitary glands. Sedimentation studies carried out on this preparation (148) reveal complete homogeneity in alkaline solutions, as observed in the ultracentrifuge. The molecular weight of the hormone has been computed to be 49,200.

The interesting investigations of physiological and biochemical effects of the growth hormone, carried out by the California group in Evans' laboratory, are too numerous (149 to 157) to describe, but serve as a model of careful exploitation of a new tool. Two reviews of this work are available (158, 159). Li concludes (159) that growth hormone is a protein anabolic factor, and that it has been shown to (a) retain urinary nitrogen, (b) lower blood amino acid concentrations, (c) elevate protein content and decrease fat content in the carcass, thymus, and liver, (d) elevate blood alkaline phosphatase and inorganic phosphate levels, (e) elevate the ribonucleic acid content of the liver, and (f) enhance amino acid uptake into protein in the skeletal muscle. Through what mechanisms growth hormone performs these protein anabolic functions is not as yet known. It would appear profitable to devise experiments in which its action on biological peptide bond synthesis might be investigated. Friedberg & Greenberg (160, 40) have, in the initial report on this type of study, presented evidence that growth hormone induces an increased protein metabolism in skeletal muscle. The incorporation of  $S^{35}$  from labeled methionine into the protein of skeletal muscle six hr. after its injection in the animal was increased about 70 per cent by administration of growth hormone. On the other hand, liver showed no such marked increase in amino acid uptake under the influence of growth hormone. The possibility of testing the effect of growth hormone on in-

corporation of amino acid into slice proteins of various tissues has not been reported as yet in the literature.

The physiological effects of long-continued administration of growth hormone to rats are more glamorous to relate than are the biochemical effects. The injected rats continued to gain weight and to grow in skeletal size (151) for over a year, though injections were not started in the rats until a growth plateau had been reached in the young adult period of their life span. There was a generalized increase in size of the rat skull, and a disproportionately great increase in growth of the mandible (152). Histologically, the mandibular condyle showed a marked growth response which resulted in enlargement and in most cases in distortion. Thus, a characteristic feature of human acromegaly is mimicked, and the relation of this sign of the human disease to the effect of growth hormone is demonstrated experimentally.

In the fasting rat, purified growth hormone has been found by Szego & White (161) to produce a nitrogen sparing effect accompanied by an acceleration of fat metabolism. Chow & Greep (162) show that the quality of proteins in the diet can affect the growth of hypophysectomized rats, and that this factor must be evaluated in the assay of growth hormone preparations. Frazer *et al.* (163) state, on the basis of negative experiments on pregnant rats, that either growth hormone fails to pass the placental barrier or else fails to excite fetal growth.

In contrast to the protein anabolic functions of growth hormone, adrenocorticotrophic hormone (ACTH) has been found to raise the level of blood amino acids and to enhance urinary excretion of nitrogen and potassium in rats (153). Whether the so-called protein catabolic function of ACTH is to be explained on the basis of decreased protein synthesis or increased protein degradation, however, remains undecided (164).

The subject of the regulatory function of the adrenal cortex, and the influence of adrenocorticotrophic hormone on cortical secretion has been well reviewed by Long (165) and more recently has been the subject of a symposium (166). Particularly pertinent to the problems of protein metabolism are the findings of White & Dougherty [reviewed by White (167)] that the cortical hormones or the adrenocorticotrophic hormone when injected into normal animals bring about a rapid cytolysis of lymphocytes in the lymphoid tissues. A rise in total serum globulin as a result of this re-

lease of lymphoid cell protein may be demonstrated by electrophoresis. Since the gamma globulins carry specific immune bodies, the titer of specific antibodies in the serum has been found to rise following injection of cortical hormone. As in the case of the growth hormone, it must again be pointed out that the mechanism of biochemical action of the adrenal cortical hormones on the lymphoid cell membrane is unknown, nor can it be stated with certainty whether the effect is a direct one or an indirect one operating through the mediation of other factors.

Some progress has been made on the problem of defining the biochemical effect of testosterone on protein metabolism. Samuels and colleagues (168, 169) report that methyltestosterone accelerates the synthesis of guanidoacetic acid, which in turn is methylated to creatine. The findings of Hoberman *et al.* (170) are in essential agreement. Sims (171) later reports in a feeding study on a human that the sole action of methyltestosterone on creatine metabolism is in acceleration of guanidoacetic acid synthesis. Sweat & Samuels (169) further find that the testosterone-destroying mechanism of liver involves an oxidative enzyme and that diphosphopyridine nucleotide and citrate accelerate the rate of destruction of testosterone by rat liver minces. These observations provide the first intimate relationship to be uncovered between the steroid hormones and the machinery of intermediary metabolism, and are an event for rejoicing. Another finding of some biochemical interest with respect to the action of steroids is the reported isolation by Lowenstein [reported by Sayers *et al.* (172)] from the adrenal cortex of a water soluble and biologically active steroid in which the steroid nucleus is linked with ascorbic acid.

Taurog & Chaikoff (173) present evidence that the circulating thyroid hormone in the normal animal consists of thyroxine loosely attached to plasma protein. They find that when crystalline thyroxine is added to plasma, it behaves like naturally occurring protein-bound iodine of plasma in a number of respects, including its lack of dialyzability.

Wislocki, Aub & Waldo (174) have attempted to analyze by experimental means the factors controlling the annual renewal, growth, and shedding of deer antlers. They have found that castration of Virginia deer in the first eight months of life results in complete suppression of antler growth. Castration after the appearance of the first set of antlers, if the antlers are in the velvet,

results in the permanent retention of the velvet and failure of the antlers to be shed. Castration, in the presence of antlers which have lost their velvet, results in immediate shedding of the antlers and their subsequent renewal and permanent retention the following year. Administration of testosterone provides adequate substitution therapy for antler growth. The effects of castration indicate the existence of an hypophyseal factor responsible for antler growth, and a testicular factor responsible mainly for secondary hardening of the antlers and loss of velvet. These two factors appear to alternate and supplement each other in regulating antler growth and maturation.

#### NEOPLASIA AS RELATED TO PROTEIN METABOLISM

A thoughtful and stimulating review of neoplastic abnormal growth was made by Rhoads (175), in 1949. A sentence from his concluding paragraph states that

one fact stands out as worthy of special mention from the vast collection of factual material existent on neoplastic growth—that is that further data are urgently required on the comparative compositions of normal and neoplastic cells. These data may concern genes, enzymes, proteins, or any other component. It is important to prove only that the component is different from any normal component and to learn how to accomplish its destruction.

To recast this general thought in its relation to protein metabolism and growth, it is important to search for growth control mechanisms which regulate the protein metabolism of normal cells, and which fail to operate effectively in malignant cells. It may be useful to enumerate some of the limitations of our knowledge of this subject. The pituitary, adrenal, and testicular hormones influence protein metabolism, but their mechanism of action remains to be worked out. The amino acid blood levels and their concentrations relative to one another affect regulation of the transport of these protein building blocks across the cell membrane, but whether there is an alteration in the neoplastic cell remains to be seen.

That nucleic acids and their building stones have a profound effect on protein metabolism is clear, but the point of connection is obscure. The growth promoting and inhibiting properties of embryo extract and of serum of aged animals on tissue cultures have been known for many years, but the explanation of these

effects is still largely wanting. Much of Greenstein's valuable work (176) has been concerned with collection of enzymatic fingerprints of malignant tissues and their normal counterparts. Unfortunately, it may be that the very enzyme systems which it would be most valuable to compare are those which are as yet unidentified. In general, the mechanisms of synthetic reactions closely allied to cell growth have eluded description up to the present time. This applies to protein, nucleic acid, and lipid synthesis in particular. It is to be expected that enzymatic reactions requiring the input of energy may be more complex to unravel than the degradative, hydrolytic ones which have largely been studied in comparisons of normal and malignant tissues. Yet it would appear that part of the biochemical advantage of the malignant cell over its normal counterpart is its ability to synthesize constituents for new cells at a rate in excess of the normal.

In the face of this dilemma, a number of investigators have stepped back a pace from the close-up but fragmentary view of cell growth kinetics afforded by a comparison of known enzyme systems. They have begun to make systematic studies of cell reaction mechanisms, using labeled substrates such as amino acids (88, 89, 90, 177), purines (178), and carbohydrate intermediates (179), with an eye toward uncovering a difference between normal and malignant cells. Winnick *et al.* (88), and Reid & Jones (89) have studied the distribution of  $C^{14}$ -labeled DL-tyrosine in the tissues of tumor-bearing rats and mice respectively. Kremen *et al.* (90) used  $S^{35}$ -labeled methionine in a similar investigation. In these several studies, the tumors incorporated the amino acid into their proteins at a rapid rate, which was, however, exceeded by the specific activity found in such tissues as adrenal, intestinal mucosa, kidney, and thyroid. Zamecnik *et al.* (177) used a slice technique, and compared the rate of incorporation of  $C^{14}$ -labeled DL-alanine and glycine into the proteins of surviving normal liver and hepatoma slices. The rate of incorporation of alanine into the hepatoma slice protein was six times that found in the normal slice protein. The findings with respect to glycine were similar. These data imply that the rate of protein synthesis in the surviving hepatoma slice exceeds that in the normal liver slice. Further experiments (55) indicate that the hepatoma slices fix  $C^{14}O_2$  into proteins at a rate in excess of that of normal slices, when pyruvate is added to the slice media. Thus, in two respects the malignant

tissue appears to have a biochemical advantage over its normal counterpart.

It is suggested from the above experiments that, in general, labeled amino acids are incorporated into tissue proteins at rates in keeping with the metabolic rates of the tissues. In a tissue where protein is synthesized for distribution to the body as a whole, however, the rate of incorporation also reflects this added protein manufacturing function.

Greenstein (176) has found that for the majority of enzymes investigated, the activity in neoplastic tissue has been less than that found in its normal counterpart. The possibility has been raised that neoplastic tissue might be unable to construct particular types of protein, possibly due to a failure to build a particular amino acid into the peptide chain. Comparisons of the amino acid composition of their proteins have, however, revealed little difference (55, 180) between normal and malignant tissues. The free intracellular amino acid concentration of certain tumors has, however, been found by Roberts & Tishkoff (23) to be different from that of normal tissues.

A discrete step forward in linking chemical carcinogenesis with protein metabolism has been made by the Millers and co-workers (181, 182, 183). They find that the carcinogenic azo dye *p*-dimethylaminoazobenzene is selectively bound to liver protein and can only be separated from protein by vigorous hydrolytic procedures. This promising lead is being actively pursued by fractionation of the involved liver proteins and by studies on the effect of structural alteration of the dye molecule on its binding properties (184). Despite this intensive study, it cannot be stated whether the parent compound or its degradation products are responsible for the carcinogenic property. The relationship of this compound to riboflavin metabolism is certainly an important one, and it would appear desirable for someone to make a systematic study of the effect of this dye on enzyme systems in the rat liver which are activated by coenzymes of which riboflavin is a part. L-Amino acid oxidase is one such enzyme which would have an obvious relationship to protein metabolism, and yet little attention has been paid to the possibility that the azo dye carcinogens may interfere with operation of this enzyme. Kensler (185) has recently reported that the carcinogen *p*-dimethylaminoazobenzene does reduce the hepatic riboflavin level. The California group in Luck's laboratory

has found that as *m'*-methyl-*p*-dimethylaminoazobenzene was fed, the concentration of desoxyribonucleoproteins in the liver increased (186), the gamma-globulin concentration in the blood serum rose, and the albumin concentration fell (187).

In this latter connection, Huggins *et al.* (188) have devised a cancer diagnostic screen test based on a qualitative defect in the proteins of the serum found to occur in a large percentage of cases of human cancer. Huggins points out that the defect is not specific, and reactions similar to that in cancer have been obtained in the presence of pulmonary tuberculosis and some acute massive inflammatory processes as well.

Tannenbaum & Silverstone (189) continue to pursue the relationship of diet to the genesis of tumors. One interesting facet of their recent observations is the finding that the incidence of spontaneous hepatomas was significantly lower in mice fed 9 per cent casein than in those given 18 per cent or higher proportions of casein.

One of the bright chemotherapeutic leads of the year originated from a study of the nutritional requirements of *Tetrahymena*. Kidder *et al.* (190) point out that mammals "can synthesize guanine from adenine, but cannot make use of dietary guanine for the reverse reaction. *Tetrahymena*, on the other hand, cannot synthesize guanine but requires this purine in the diet." It occurred to these investigators that neoplastic tissue might also conceivably have lost its ability to synthesize guanine. If such were the case, a guanine analogue might selectively inhibit the neoplastic cell. Injection of mice bearing a transplantable mouse mammary adenocarcinoma, a spontaneous mammary carcinoma, and a lymphoid leukemia with a guanine analogue, 5-amino-7-hydroxy-1H-v-triazolo-(D)-pyrimidine resulted in cessation of growth but not death of these tumors. Clearly this work will have to be expanded to other types of neoplasia.

A highly interesting development in the relations of hormones to cancer is mentioned cautiously by Evans *et al.* (191) in a paper on the effects of pituitary growth hormone on body growth of rats. After injection, started in six month old female rats, over a year's time with purified growth hormone, a general somatic growth of the rats was observed. Of eight injected rats, tumors of mammary origin (fibromata or adenofibromata) were observed in three. None occurred in the uninjected controls. A large fibrous subdia-

phragmatic tumor, three small ovarian tumors, and a large adrenal tumor were also found in the injected group. It was pointed out that spontaneous tumors occur in old normal females of the Long-Evans strain. Three tumors were found in the controls of this small series. The authors state that there appeared to be an increased incidence of tumors in the experimental animals, but stress the need for a larger series.

#### CONCLUSION

The reviewers have been struck by the increase in mingling and merging of traditionally separate disciplines in recent investigations on the problems of growth. Biochemists have been found using genetic tools, and nutritionists dipping into bacteriology, to quote examples.

As the living organism increases in complexity, so necessarily do the mechanisms which control and regulate its orderly growth. A new word, cybernetics, has been coined (192) to describe this over-all concept that in the living machine there exist feed-back mechanisms which, in response to messages received through the system, relay back instructions that modify the performance of the system. In the new terminology, therefore, neoplasia or any abnormal growth might be considered as a problem in faulty cybernetics.

## LITERATURE CITED

1. *The Chemistry and Physiology of Growth*, 293 pp. (Parpart, A. K., Ed. Princeton Univ. Press, Princeton, N. J., 1949)
2. *Symposia of the Society for Experimental Biology, No. II, Growth in Relation to Differentiation and Morphogenesis*, 365 pp. (Academic Press, Inc., New York, 1948)
3. Eighth Symposium on Development and Growth, *Growth*, **12**, Suppl., 3-200 (1948)
4. *Symposia of the Society for Experimental Biology, No. I, Nucleic Acid*, 290 pp. (Cambridge Univ. Press, Cambridge, 1947)
5. KOSER, S. A., *Ann. Rev. Microbiol.* **2**, 121-42 (1948)
6. GALE, E. F., *The Chemical Activities of Bacteria*, 199 pp. (Academic Press, Inc., New York, 1948)
7. CANNON, P. R., *Some Pathogenic Consequences of Protein and Amino Acid Deficiencies*, 49 pp. (Charles C Thomas, Springfield, Ill., 1948)
8. MOORE, S., AND STEIN, W. H., *Ann. N. Y. Acad. Sci.* **49**, 265-78 (1948)
9. STEIN, W. H., AND MOORE, S., *J. Biol. Chem.*, **176**, 337-65 (1948)
10. MOORE, S., AND STEIN, W. H., *J. Biol. Chem.*, **176**, 367-88 (1948)
11. STEIN, W. H., AND MOORE, S., *J. Biol. Chem.*, **178**, 79-91 (1949)
12. MOORE, S., AND STEIN, W. H., *J. Biol. Chem.*, **178**, 53-77 (1949)
13. GORDON, A. H., MARTIN, A. J. P., AND SYNGE, R. L. M., *Biochem. J.*, **37**, 79-86 (1943)
14. MARTIN, A. J. P., AND SYNGE, R. L. M., *Biochem. J.*, **35**, 1358-68 (1941)
15. ELSDEN, S. R., AND SYNGE, R. L. M., *Biochem. J.*, **38**, ix (1944)
16. BORSOOK, H., DEASY, C. L., HAAGEN-SMIT, A. J., KEIGHLEY, G., AND LOWY, P. H., *J. Biol. Chem.*, **174**, 1041-42 (1948)
17. FRANTZ, I. D., JR., LOFTFIELD, R. B., AND WERNER, A. S., *Federation Proc.*, **8**, 199 (1949)
18. DALY, M. M., AND MIRSKY, A. E., *J. Biol. Chem.*, **179**, 981-82 (1949)
19. COHN, W. E., *Science*, **109**, 377-78 (1949)
20. STEIN, W. H., AND MOORE, S., *Cold Spring Harbor Symposia Quant. Biol.* (In press)
21. BARRY, G. T., GREGORY, J. D., CRAIG, L. C., *J. Biol. Chem.*, **175**, 485-86 (1948)
22. DENT, C. E., STEPKA, W., AND STEWARD, F. C., *Nature*, **160**, 682-83 (1947)
23. ROBERTS, E., AND TISHKOFF, G. H., *Science*, **109**, 14-16 (1949)
24. HAUGAARD, G., AND KRONER, T. D., *J. Am. Chem. Soc.*, **70**, 2135-37 (1948)
25. AWAPARA, J., *J. Biol. Chem.*, **178**, 113-16 (1949)
26. Paper Partition Chromatography, *Nutrition Revs.*, **7**, 195-98 (1949)
27. RANDALL, S. S., AND MARTIN, A. J. P., *Biochem. J.*, **44**, ii (1949)
28. DARMON, S. E., SUTHERLAND, G. B. B. M., AND TRISTRAM, G. R., *Biochem. J.*, **42**, 508-16 (1948)
29. BRAND, E., *Ann. N. Y. Acad. Sci.*, **47**, 187-228 (1946)
30. DUNN, M. S., FEAVER, E. R., AND MURPHY, E. A., *Can. Research*, **9**, 306-13 (1949)
31. BOYD, M. J., LOGAN, M. A., AND TYTELL, A. A., *J. Biol. Chem.* **174**, 1027-35 (1948)

32. BONNER, D. M., *Science*, **108**, 735-39 (1948)
33. VAN NIEL, C. B., *The Chemistry and Physiology of Growth* 91-105 (Parpart, A. K., Ed., Princeton Univ. Press, Princeton, N. J., 1949)
34. MELCHIOR, J. B., AND TARVER, H., *Arch. Biochem.*, **12**, 301-8 (1947)
35. MELCHIOR, J. B., AND TARVER, H., *Arch. Biochem.*, **12**, 309-15 (1947)
36. ANFENSEN, C. B., BELOFF, A., HASTINGS, A. B., AND SOLOMON, A. K., *J. Biol. Chem.*, **168**, 771-72 (1947)
37. EHRENSVARD, G., *Cold Spring Harbor Symposia Quant. Biol.*, **13**, 81-87 (1948)
38. WINNICK, T., FRIEDBERG, F., AND GREENBERG, D. M., *Arch. Biochem.*, **15**, 160-61 (1947)
39. FRANTZ, I. D., JR., LOFTFIELD, R. B., AND MILLER, W. W., *Science*, **106**, 544-45 (1947)
40. GREENBERG, D. M., FRIEDBERG, F., SCHULMAN, M. P., AND WINNICK, T., *Cold Spring Harbor Symposia Quant. Biol.*, **13**, 113-17 (1948)
41. ANFENSEN, C. B., BELOFF, A., AND SOLOMON, A. K., *J. Biol. Chem.*, **179**, 1001-13 (1949)
42. TOLBERT, B. M., *J. Biol. Chem.*, **173**, 205-6 (1948)
43. WINNICK, T., FRIEDBERG, F., AND GREENBERG, D. M., *J. Biol. Chem.*, **175**, 117-26 (1948)
44. WINNICK, T., MORING-CLAESON, I., AND GREENBERG, D. M., *J. Biol. Chem.*, **175**, 127-32 (1948)
45. BORSOOK, H., DEASY, C. L., HAAGEN-SMIT, A. J., KEIGHLEY, G., AND LOWY, P. H., *J. Biol. Chem.*, **179**, 689-704 (1949)
46. KESTON, A. S., *Cold Spring Harbor Symposia Quant. Biol.* (In press)
47. FRIEDBERG, F., WINNICK, T., AND GREENBERG, D. M., *J. Biol. Chem.*, **169**, 763-64 (1947)
48. BORSOOK, H., DEASY, C. L., HAAGEN-SMIT, A. J., KEIGHLEY, G., AND LOWY, P. H., *J. Biol. Chem.*, **179**, 705-19 (1949)
49. BLOCH, K., *J. Biol. Chem.*, **179**, 1245-54 (1949)
50. LIPMANN, F., *Advances in Enzymology and Related Subjects* **1**, 99-162 (Interscience Publishers, N. Y., 1941)
51. FRANTZ, I. D., JR., ZAMECNIK, P. C., REESE, J. W., AND STEPHENSON, M. L., *J. Biol. Chem.*, **174**, 773-74 (1948)
52. SPECK, J. F., *J. Biol. Chem.*, **179**, 1405-26 (1949)
53. SIMMONDS, S., TATUM, E. L., AND FRUTON, J. S., *J. Biol. Chem.*, **170**, 483-89 (1947)
54. SIMMONDS, S., AND FRUTON, J. S., *Science*, **109**, 561-62 (1949)
55. ZAMECNIK, P. C., AND FRANTZ, I. D., JR., *Cold Spring Harbor Symposia Quant. Biol.* (In press)
56. AXELROD, B., *J. Biol. Chem.*, **172**, 1-13 (1948)
57. AXELROD, B., *J. Biol. Chem.*, **176**, 295-98 (1948)
58. LONDON, I. M., SHEMAIN, D., WEST, R., AND RITTENBERG, D., *J. Biol. Chem.*, **179**, 463-84 (1949)
59. GRINSTEIN, M., ALDRICH, R. A., HAWKINSON, V., AND WATSON, C. J., *J. Biol. Chem.*, **179**, 983-84 (1949)
60. WITTENBERG, J., AND SHEMAIN, D., *J. Biol. Chem.*, **178**, 47-51 (1949)

61. SHEMIN, D., *Cold Spring Harbor Symposia Quant. Biol.*, **13**, 185-92 (1948)
62. ALTMAN, K. I., SALOMON, K., AND NOONAN, T. R., *J. Biol. Chem.*, **177**, 489-90 (1949)
63. RITTENBERG, D., *Cold Spring Harbor Symposia Quant. Biol.*, **13**, 173-79 (1948)
64. SCHUBERT, J., AND ARMSTRONG, W. D., *J. Biol. Chem.*, **177**, 521-27 (1949)
65. CASPERSSON, T., *Symposia of the Society for Experimental Biology, No. 1, Nucleic Acid*, 127-51 (Cambridge Univ. Press, Cambridge, 1947)
66. STEPKA, W., BENSON, A. A., AND CALVIN, M., *Science*, **108**, 304 (1948)
67. FRANTZ, I. D., JR., AND FEIGELMAN, H., *Cancer Research*, **9**, 619 (1949)
68. SHEMIN, D., *J. Biol. Chem.*, **162**, 297-307 (1946)
69. SAKAMI, W., *J. Biol. Chem.*, **176**, 995-96 (1948)
70. LICHSTEIN, H. C., *J. Biol. Chem.*, **177**, 487-88 (1949)
71. COHEN, P. P., AND GRISOLIA, S., *J. Biol. Chem.*, **174**, 389-90 (1948)
72. RATNER, S., AND PAPPAS, A., *J. Biol. Chem.*, **179**, 1183-98 (1949)
73. KREBS, H. A., EGGLESTON, L. V., AND HEMS, R., *Biochem. J.*, **43**, 406-13 (1948)
74. MILLER, L. L., *Federation Proc.*, **8**, 229-30 (1949)
75. MILLER, L. L., AND BALE, W. F., *Federation Proc.*, **8**, 230 (1949)
76. BORSOOK, H., DEASY, C. L., HAAGEN-SMIT, A. J., KEIGHLEY, G., AND LOWY, P. H., *J. Biol. Chem.*, **176**, 1383-93 (1948)
77. BORSOOK, H., DEASY, C. L., HAAGEN-SMIT, A. J., KEIGHLEY, G., AND LOWY, P. H., *J. Biol. Chem.*, **176**, 1395-1400 (1948)
78. EMERSON, S., *Cold Spring Harbor Symposia Quant. Biol.* (In press)
79. GALE, E. F., AND TAYLOR, E. S., *J. Gen. Microbiol.*, **1**, 314-26 (1947)
80. GALE, E. F., AND RODWELL, A. W., *J. Bact.*, **55**, 161-67 (1948)
81. CHRISTENSEN, H. N., AND STREICHER, J. A., *J. Biol. Chem.*, **175**, 95-100 (1948)
82. CHRISTENSEN, H. N., ROTHWELL, J. T., SEARS, R. A., AND STREICHER, J. A., *J. Biol. Chem.*, **175**, 101-5 (1948)
83. CHRISTENSEN, H. N., STREICHER, J. A., AND ELBINGER, R. L., *J. Biol. Chem.*, **172**, 515-24 (1948)
84. CHRISTENSEN, H. N., *Federation Proc.*, **8**, 190 (1949)
85. KREBS, H. A., AND EGGLESTON, L. V., *Biochem. J.*, **44**, vii (1949)
86. AWAPARA, J., AND MARVIN, H. N., *J. Biol. Chem.*, **178**, 691-93 (1949)
87. AWAPARA, J., MARVIN, H. N., AND WELLS, B. B., *Endocrinology*, **44**, 378-83 (1949)
88. WINNICK, T., FRIEDBERG, F., AND GREENBERG, D. M., *J. Biol. Chem.*, **173**, 189-97 (1948)
89. REID, J. C., AND JONES, H. B., *J. Biol. Chem.*, **174**, 427-37 (1948)
90. KREMEN, A. J., HUNTER, S. W., MOORE, G. E., AND HITCHCOCK, C. R., *Cancer Research*, **9**, 174-76 (1949)
91. MAASS, A. R., LARSON, F. C., AND GORDON, E. S., *J. Biol. Chem.*, **177**, 209-16 (1949)
92. WOOLLEY, D. W., *Growth*, **12**, Suppl., 3-16 (1948)
93. SHIVE, W., EAKIN, R. E., HARDING, W. M., RAVEL, J. M., AND SUTHERLAND, J. E., *J. Am. Chem. Soc.*, **70**, 2299 (1948)

94. KIDDER, G. W., DEWEY, V. C., AND PARKS, R. E., JR., *Science*, **109**, 511-14 (1949)
95. ROCKLAND, L. B., AND DUNN, M. S., *J. Biol. Chem.*, **179**, 511-21 (1949)
96. FRAENKEL, G., BLEWETT, M., AND COLES, M., *Nature*, **161**, 981-83 (1948)
97. Choline Requirement of the German Cockroach, *Nutrition Revs.*, **7**, 219-20 (1949)
98. HUTNER, S. H., PROVASOLI, L., STOKSTAD, E. L. R., HOFFMANN, C. E., BELT, M., FRANKLIN, A. L., JUKES, T. H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 118-20 (1949)
99. Usefulness of Stress in Experimental Nutrition Studies, *Nutrition Revs.*, **7**, 75-78 (1949)
100. ROSE, W. C., *Physiol. Revs.*, **18**, 109-36 (1938)
101. ROSE, W. C., OESTERLING, M. J., AND WOMACK, M., *J. Biol. Chem.*, **176**, 753-62 (1948)
102. KREBS, H. A., EGGLESTON, L. V., AND HEMS, R., *Biochem. J.*, **44**, 159-63 (1949)
103. McILWAIN, H., ROPER, J. A., AND HUGHES, D. E., *Biochem. J.*, **42**, 492-508 (1948)
104. ROPER, J. A., AND McILWAIN, H., *Biochem. J.*, **42**, 485-92 (1948)
105. MAYER, J., *Growth*, **12**, 341-49 (1948)
106. DUNN, M. S., MURPHY, E. A., AND ROCKLAND, L. B., *Physiol. Revs.*, **27**, 72-94 (1947)
107. CANNON, P. R., *Nutrition Revs.*, **7**, 161-64 (1949)
108. CANNON, P. R., *J. Am. Dietet. Assoc.*, **24**, 937-38 (1948)
109. PEARCE, E. L., SAUBERLICH, H. E., AND BAUMANN, C. A., *J. Biol. Chem.*, **168**, 271-82 (1947)
110. SAUBERLICH, H. E., AND BAUMANN, C. A., *Arch. Biochem.*, **20**, 305-14 (1949)
111. MADDY, K. H., AND ELVEHJEM, C. A., *J. Biol. Chem.*, **177**, 577-90 (1949)
112. Assay of "Animal Protein Factor" Using Mice, *Nutrition Revs.*, **7**, 167-69 (1949)
113. Protogen: a New Growth Factor, *Nutrition Revs.*, **7**, 207-8 (1949)
114. Assay and Distribution of Vitamin B<sub>12</sub>, *Nutrition Revs.*, **7**, 210-11 (1949)
115. Growth-promoting Action of Vitamin B<sub>12</sub> in Rations Containing Iodinated Protein, *Nutrition Revs.*, **7**, 183-84 (1949)
116. Vitamin B<sub>12</sub>, Folic Acid, and Thymidine, *Nutrition Revs.*, **7**, 19-20 (1949)
117. Vitamin B<sub>12</sub>, *Nutrition Revs.*, **7**, 164-66 (1949)
118. Activity of Microbial Animal Factor Concentrates in Pernicious Anemia, *Nutrition Revs.*, **7**, 10-11 (1949)
119. BOSSHARDT, D. K., PAUL, W. J., O'DOHERTY, K., HUFF, J. W., AND BARNES, R. H., *J. Nutrition*, **37**, 21-35 (1949)
120. BEADLE, G. W., *Harvey Lectures, Ser. XL*, 179-94 (1944-45)
121. Fanconi's Syndrome, *Nutrition Revs.*, **7**, 24-25 (1949)
122. WOOLLEY, D. W., *Physiol. Revs.*, **27**, 308-34 (1947)
123. BRICKSON, W. L., HENDERSON, L. M., SOLHJELL, I., AND ELVEHJEM, C. A., *J. Biol. Chem.*, **176**, 517-28 (1948)
124. HARDING, W. M., AND SHIVE, W., *J. Biol. Chem.*, **174**, 743-55 (1948)
125. ROGERS, L. L., AND SHIVE, W., *J. Biol. Chem.*, **172**, 751-58 (1948)

126. HITCHINGS, G. H., ELION, G. B., AND VANDER WERFF, H., *J. Biol. Chem.*, **174**, 1037-38 (1948)
127. KOBAYASHI, Y., FLING, M., AND FOX, S. W., *J. Biol. Chem.*, **174**, 391-98 (1948)
128. BUBL, E. C., AND BUTTS, J. S., *J. Biol. Chem.*, **174**, 637-42 (1948)
129. WOOLLEY, D. W., *Physiol. Revs.*, **27**, 308-33 (1947)
130. BOREK, E., AND WAELSCH, H., *J. Biol. Chem.*, **177**, 135-41 (1949)
131. FERGER, M. F., AND VIGNEAUD, V. DU, *J. Biol. Chem.*, **174**, 241-46 (1948)
132. FRIEDEN, E., AND WINZLER, R. J., *J. Biol. Chem.*, **176**, 155-63 (1948)
133. CRAIG, L. C., GREGORY, J. D., AND BARRY, G. T., *Cold Spring Harbor Symposia Quant. Biol.* (In press)
134. WOOLLEY, D. W., *J. Biol. Chem.*, **176**, 1291-98 (1948)
135. WOOLLEY, D. W., *J. Biol. Chem.*, **176**, 1299-1308 (1948)
136. WHITE, P. R., *Ann. N. Y. Acad. Sci.*, **49**, 111-18 (1947)
137. FISCHER, A., *Biochem. J.*, **43**, 491-97 (1948)
138. SANFORD, K. K., EARLE, W. R., AND LIKELY, G. D., *J. Nat. Cancer Inst.*, **9**, 229-46 (1948)
139. GEY, G. O., HANKS, J. H., AND BARRETT, R., *Growth*, **12**, 69-105 (1948)
140. GAILLARD, P. J., *Symposia of the Society for Experimental Biology, No. II, Growth in Relation to Differentiation and Morphogenesis*, 139-44 (Academic Press, Inc., N. Y., 1948)
141. BRUES, A. M., AND NARANJO, A., *Anat. Record*, **100**, 12-13 (1948)
142. ZAMECNIK, P. C., FRANTZ, I. D., JR., AND STEPHENSON, M. L., *Cancer Research*, **9**, 612-13 (1949)
143. LI, C. H., EVANS, H. M., AND SIMPSON, M. E., *Science*, **108**, 624 (1948)
144. PRICE, W. H., CORI, C. F., COLOWICK, S. P., *J. Biol. Chem.*, **160**, 633-34 (1945)
145. LI, C. H., AND MOSKOWITZ, M., *J. Biol. Chem.*, **178**, 203-5 (1949)
146. LI, C. H., SIMPSON, M. E., AND EVANS, H. M., *Science*, **109**, 445-46 (1949)
147. WILHELMI, A. E., FISHMAN, J. B., AND RUSSELL, J. A., *J. Biol. Chem.*, **176**, 735-45 (1948)
148. SMITH, E. L., BROWN, D. M., FISHMAN, J. B., *J. Biol. Chem.*, **177**, 305-10 (1949)
149. LI, C. H., SIMPSON, M. E., AND EVANS, H. M., *Growth*, **12**, 39-42 (1948)
150. KONEFF, A. A., SIMPSON, M. E., EVANS, H. M., AND LI, C. H., *Growth*, **12**, 33-37 (1948)
151. EVANS, H. M., BECKS, H., ASLING, C. W., SIMPSON, M. E., AND LI, C. H., *Growth*, **12**, 43-54 (1948)
152. BECKS, H., COLLINS, D. A., ASLING, C. W., SIMPSON, M. E., LI, C. H., AND EVANS, H. M., *Growth*, **12**, 55-67 (1948)
153. LI, C. H., GESCHWIND, I., AND EVANS, H. M., *J. Biol. Chem.*, **177**, 91-95 (1949)
154. LI, C. H., INGLE, D. J., PRESTRUD, M. C., AND NEZAMIS, J. E., *Endocrinology*, **44**, 454-57 (1949)
155. LI, C. H., SIMPSON, M. E., AND EVANS, H. M., *Endocrinology*, **44**, 71-75 (1949)

156. GORDON, G. S., BENNETT, L. L., LI, C. H., AND EVANS, H. M., *Endocrinology*, **42**, 153-60 (1948)
157. KINSELL, L. W., MICHAELS, G. D., LI, C. H., AND LARSEN, W. E., *J. Clin. Endocrinol.*, **8**, 1013-36 (1948)
158. LI, C. H., AND EVANS, H. M., in *Vitamins and Hormones*, **5**, 197-231 (Harris, R. S., and Thimann, K. V., Eds., Academic Press, Inc., New York, 1947)
159. LI, C. H., *Growth*, **12**, Suppl., 47-60 (1948)
160. FRIEDBERG, F., AND GREENBERG, D. M., *Arch. Biochem.*, **17**, 193-95 (1948)
161. SZEGO, C. M., AND WHITE, A., *Endocrinology*, **44**, 150-66 (1949)
162. CHOW, B. F., AND GREEP, R. O., *Proc. Soc. Exptl. Biol. Med.*, **69**, 191-92 (1948)
163. FRAZER, J. F. D., HUGGETT, A. ST. G., AND WOHLZOGEN, F. X., *J. Physiol. (London)*, **108**, 44P (1949)
164. RUSSELL, J. A., AND CAPIELLO, M., *Endocrinology*, **44**, 333-44 (1949)
165. LONG, C. N. H., *The Chemistry and Physiology of Growth*, 266-84 (Parpart, A. K., Ed., Princeton Univ. Press, Princeton, N. J., 1949)
166. The Adrenal Cortex, *Ann. N. Y. Acad. Sci.*, **50**, 509-678 (1949)
167. WHITE, A., *Harvey Lectures* (In press)
168. LEVENDAH, B. H., AND SAMUELS, L. T., *J. Biol. Chem.*, **176**, 327-36 (1948)
169. SWEAT, M. L., AND SAMUELS, L. T., *J. Biol. Chem.*, **175**, 1-5 (1948)
170. HOBERMAN, H. D., SIMS, E. A. H., AND ENGSTROM, W. W., *J. Biol. Chem.*, **173**, 111-16 (1948)
171. SIMS, E. A. H., *Am. J. Physiol.*, **157**, 404-411 (1949)
172. SAYERS, G., SAYERS, M. A., LIANG, T. Y., AND LONG, C. N. H., *Endocrinology*, **38**, 1-9 (1946)
173. TAUROG, A., AND CHAIKOFF, I. L., *J. Biol. Chem.*, **176**, 639-56 (1948)
174. WISLOCKI, G. B., AUB, J. C., AND WALDO, C. M., *Endocrinology*, **40**, 202-24 (1947)
175. RHODES, C. P., *The Chemistry and Physiology of Growth*, 217-65 (Parpart, A. K., Ed., Princeton Univ. Press, Princeton, N. J., 1949)
176. GREENSTEIN, J. P., *Biochemistry of Cancer*, 389 pp. (Academic Press, Inc., New York, 1947)
177. ZAMECNIK, P. C., FRANTZ, I. D., JR., LOFTFIELD, R. B., AND STEPHENSON, M. L., *J. Biol. Chem.*, **175**, 299-314 (1948)
178. BROWN, G. B., *Cold Spring Harbor Symposia Quant. Biol.*, **13**, 43-51 (1948)
179. OLSON, R. E., AND STARE, F. J., *Federation Proc.*, **8**, 391-92 (1949)
180. DUNN, M. S., FEAVER, E. R., AND MURPHY, E. A., *Cancer Research*, **9**, 306-13 (1949)
181. MILLER, E. C., AND MILLER, J. A., *Cancer Research*, **7**, 468-80 (1947)
182. MILLER, E. C., MILLER, J. A., SAPP, R. W., AND WEBER, G. M., *Cancer Research*, **9**, 336-43 (1949)
183. PRICE, J. M., MILLER, E. C., AND MILLER, J. A., *J. Biol. Chem.*, **173**, 345-53 (1948)
184. PRICE, J. M., MILLER, E. C., MILLER, J. A., AND WEBER, G. M., *Cancer Research*, **9**, 398-402 (1949)
185. KENSLER, C. J., *J. Biol. Chem.*, **179**, 1079-84 (1949)

186. GRIFFIN, A. C., NYE, W. N., NODA, L., AND LUCK, J. M., *J. Biol. Chem.*, **176**, 1225-35 (1948)
187. COOK, H. A., GRIFFIN, A. C., AND LUCK, J. M., *J. Biol. Chem.*, **177**, 373-81 (1949)
188. HUGGINS, C., MILLER, G. M., AND JENSEN, E. V., *Cancer Research*, **9**, 177-82 (1949)
189. TANNENBAUM, A., AND SILVERSTONE, H., *Cancer Research*, **9**, 162-73 (1949)
190. KIDDER, G. W., DEWEY, V. C., AND PARKS, R. E., JR., *Science*, **109**, 511-14 (1949)
191. EVANS, H. M., SIMPSON, M. E., AND LI, C. H., *Growth*, **12**, 15-32 (1948)
192. WIENER, N., *Cybernetics: or Control and Communication in the Animal and the Machine* 194 pp. (Mass. Inst. Technol. Press, Cambridge, Mass., 1948)

## THE PHYSIOLOGY OF SUPPORTING TISSUE

BY M. J. DALLEMAGNE

*Institute of Experimental Therapeutics  
University of Liège, Belgium*

Since Murray's review appeared (1), two important contributions have been added to the literature concerning supporting tissue: Weinmann & Sicher (2) dealt with various problems of physiology and pathology, while Lacroix (3) especially studied bone induction and growth. Leicester's monograph (4) is devoted to some aspects of calcification. Maynard & Smith (5) reported on mineral metabolism.

### STRUCTURE OF BONE

*Microscopic structure.*—By comparing the development of long bones in 350 different vertebrates ranging from the amphibia to man (6), it was shown that, during the prenatal stages, the structural features are common to all species (7). Differences which become manifest after birth depend upon the rate of bone development, which is a specific or racial character (8).

Structural changes occurring during growth, as well as the conditions responsible for these evolutionary features (9), were studied in dogs (10). Functional factors evoke progressive changes in the ossified tendons of birds (11). Studies were devoted to the ossification of the distal epiphysis of the rat's humerus (12), of the mandibular joint (13), and of the third metacarpal (14). The vascular channels of bone (15) and the disposition of the fibrils (16) have been demonstrated.

Arteriographic and histological studies have shown that circulation in bone follows particular rules (17).

*Submicroscopic structure.*—The birefringence of total bone is due to a combination of the optical characters of the organic and mineral parts, in accordance with pure physical laws (18). These results have been questioned (19, 20, 22). The curve of structural double refraction of bone has been determined from the mineral fraction (18, 19). A mold of the submicroscopic spaces occupied by the organic constituents has been made by means of "plexiglas" (21). The refractive index of total bone depends upon the respec-

tive proportions of organic and mineral substances (23); it varies with age and species (24).

#### GROWTH OF BONE

Embryonal grafts into the chorio-allantois survive unless they have been boiled (25). Their vessels anastomose with the pre-existing circulatory system and the explants develop in close relation to the vascular neoformation (26). Osteoclasts resulting from the fusion of several monocytes are released from the grafts (27).

Studies have been devoted to the displacement of the tendons (28) and of the nourishing artery during development of the bone (29). Reports have been made on the influence of x-rays (30) and pH on bone growth (31).

*The evocation of bone formation.*—The inductor of ossification (osteogenin) belongs neither to the lipids, nor to the steroids (32). The mechanism of its action is only the repetition of reactions occurring during the fetal stage (33). Osteogenin plays a part in periosteal osteogenesis (34). It forces hyaline cartilage transplanted into growth cartilage to function like the latter (35), and it has a role in the formation of the perichondreal ring (36). Osteogenin also determines the evolution of grafts transplanted under the renal capsule or under the skin (37). It is present in the shaft of growing bone (38) and in the bone marrow (39); the latter, when transplanted, gives rise to the formation of bone tissue (40). Nevertheless, the theory of the bone "organizer" has been criticized (25).

*Chemical and enzymatic problems of ossification.*—The latest concepts concerning the mechanism of ossification have been reviewed by Roche (41) and Moog (42). The chemical condition of calcium and phosphorus in the blood has lost some of its importance as far as ossification is concerned since it is known that the phosphorylases (43, 44, 45) can increase the local concentration of phosphoric esters from glycogen accumulated in the tissue undergoing ossification (41). By the action of phosphatase, the role of which has been reviewed (46, 47), phosphate ions are released from the phosphoric esters and temporarily fixed on the "pre-osseous" substance. This explains the variations of the ratio of calcium to phosphorus in growing bone without calling upon the theory of primary calcification, which has been criticized (48). Furthermore, *in vitro* studies of the reactions between calcium and phosphate

ions have shown that bicalcium phosphate cannot be formed in bone (49, 50). The phosphate ions then leave the pre-osseous substance as calcium ions are brought in by the blood, and tricalcium phosphate now precipitates in the organic matrix formed by polymerization of ossein (51).

The intervention of carbonic anhydrase in ossification is doubtful. Results indicating that sulfamides inhibit calcification (52) have not received support (53).

The influence of phosphates on the solubility of calcium carbonate, and vice versa, has been investigated (54). In order to clarify the process of precipitation of tricalcium phosphate, the titration curve of phosphoric acid with calcium hydroxide has been studied again in detail, as has also the nature of the precipitates appearing immediately and subsequently (55).

A physicochemical study of calcium and magnesium compounds in biological fluids has been published (56), also a report on the functional role of the decalcifying action exerted by phosphate (57). The presence of organic anions in the bone makes it interesting to determine the dissociation constants of their calcium salts (58).

Many investigators have been concerned with the histochemical detection of the phosphatases (59, 60, 61). The normal distribution of phosphatase has been demonstrated by histochemical methods (62). It has been found in the endosteum and periosteum, in the nuclei of the fibroblasts, in the collagen fibers, osteocytes, and haversian canals, but not in the organic matrix of the bone (63). During bone development, phosphatase becomes extracellular only at the sites of calcification (64, 65). Extraction methods for phosphatase have been reviewed (66). In tissue culture experiments, it was found that the addition of phosphatase extracted by Robison's method slows the development of chick embryos, by its protein impurities (67). Besides its relation to the phosphate ions involved in the process of ossification (68, 69), phosphatase influences the evolution of the tissues which are being ossified; it changes the distribution of nucleic acids in the periosteal fibroblasts evolving toward the osteoblastic stage (70) and its activity is related to the transformation of the hypertrophied cells in the growth cartilage (71, 72). Its influence on the maturation of the organic matrix has been said to be more important than its role in the precipitation of calcium salts (73). Phosphatase also

plays a part in tooth formation; it influences the histological differentiation of every organ in which it is present (74, 75) and contributes to the production of the shell in marine molluscs (76). Contrary to some previous results, it does not induce ectopic ossification when injected into muscular tissue together with calcium glycerophosphate (77). Its activity is inhibited *in vitro* by high concentrations of sulfamides (78). The role of phosphatase during the repair of bone defects has been studied again; the enzyme is elaborated by migrating cells gathering very early at the site of lesion and later by osteogenic cells, when the osteogenic fibres are being formed and joined together into trabeculae. The intensity of these phenomena is decreased by lack of vitamin C (79). Bone phosphatase is inactivated by  $\alpha$ -amino acids (80).

#### CHEMICAL NATURE OF BONE

*Bone salts.*—Dalleماغne *et al.* (84, 85) have brought new evidence in favor of their opinion concerning the chemical nature of bone salts. According to these authors, bone salts isolated after hydrolysis of the organic matrix contain  $\alpha$ -tricalcium phosphate and various carbonates not in chemical combination with one another. Phosphate and carbonates combine to form carbonato-apatite at temperature of 900°C. and in other well-determined conditions. The isomorphism of  $\alpha$ -tricalcium phosphate and apatite has again been insisted upon (81, 82, 83). Results obtained by the study of refractive indices in bone submitted to various treatments agree with those given by the examination of x-ray diffraction spectra (84, 85).

Whereas a method for preparation of pure  $\alpha$ -tricalcium phosphate has been described in detail (86), its existence has been questioned; the reaction between lime and phosphoric acid would always result in an alkaline salt, hydroxylapatite (87). In fact, depending upon the conditions of the experiment and the reagents used, one obtains  $\alpha$ -tricalcium phosphate either pure or more or less contaminated with absorbed lime (88). These results which establish beyond question the existence of pure  $\alpha$ -tricalcium phosphate (89) have been recently re-emphasized (90). Most of them have been confirmed (91). These views have been objected to on the basis that synthesis of carbonato-apatite is not possible because the size of the crystalline lattice of apatite is incompatible with the inclusion of carbonate groups; however, it should be

borne in mind that the structure of the apatites is not exactly hexagonal as was thought before. The different apatites can be differentiated from each other by minute characters of their x-ray diffraction spectrum (92).

*Organic constituents of bone.*—The organic component of bone produces a deformation of the mineral crystallites (93). The structure of the organic matrix in mammals and fishes has been discussed (94).

Besides proteins, some other organic molecules, principally citric acid (95, 96), are also present in bone. Solubility measurements have been said to show that about 10 per cent of total calcium and phosphorus is fixed by the proteinic constituents (97). A proteolytic enzyme is present in the metaphyses of young animals (98). It originates in the marrow and plays a part in the formation of the preosseous substance (99). Glycerol extracts of these bones exhibit a peptidase activity (100).

#### BONE METABOLISM STUDIED BY MEANS OF RADIOISOTOPES

The use of isotopically marked elements in the study of bone metabolism has been mentioned in many general reviews (101, 102, 103). Exchanges of mineral phosphates between blood and bone have been studied *in vitro* (104) and *in vivo* (105) on bones from normal or denervated limbs. Phosphorylcholine does not give more phosphorus to the bone than do mineral phosphates, and the replacement of phosphorus seems to be due essentially to ionic exchanges (106).

Replacement of bone salts requires at least 230 days (107), and the metabolism of phosphorus is more active than that of calcium (108). Radiostrontium follows the same physiological rules as calcium, which is not true for plutonium, yttrium, cerium (109), or uranium; the uptake of the latter element by bone tissue is not parallel to the calcification process (110). Phosphorus fed to chickens appears in the egg only one month later; it is stored in muscle and bone (111). On the contrary, intra-esophageally administered radiocalcium can be detected in the egg laid 15 min. later (112). The uptake of radiocalcium by the skeleton of the rat has been studied (113). Tyrosine, marked with one atom of radiocarbon, does not accumulate in bone (114). A new method for tissue microanalysis has also been used on bone; it is based on induced radioactivity (115).

Radiocarbon parenterally administered as carbonate is found in the mineral fraction of bone but also, to a smaller extent, in the organic substance (116). After inhalation of labeled carbon dioxide carbon is also fixed by bone (117).

The hypothesis that the isotopic composition of potassium would be different in a mineral or biological medium has not been confirmed (118).

#### INFLUENCE OF DIETARY FACTORS ON BONE

Reducing the caloric value of the diet given to rats does not produce any bone disease, but retards the process of ossification (119).

*Proteins.*—Protein insufficiency in the diet also slows bone lengthening, but the ash content remains unchanged (120).

*Lipids.*—Coconut oil has a beneficial influence on rachitic bone by improving absorption and retention of phosphorus (121).

*Calcium and phosphorus.*—Excess or deficiency of dietary calcium produces a loss of calcium and phosphorus from the entire organism (122) and reduces the ash content of bone (123). In growing animals receiving a diet made rachitogenic by excess of calcium, it has been confirmed that starvation soon causes the appearance of a positive line test (124). Severe calcium and phosphorus deficiency in the diet, as well as extensive restriction of a normal diet, produces a decrease of ash, especially in the bones of limbs paralyzed by nervous section (125).

A diet rich in phosphorus and poor in calcium lowers the Ca/P ratio in the bones of young rats; this has been interpreted as evidence in favor of the presence of dicalcium phosphate in the mineral constituents (126). Calcium carbonate added to bread can correct an otherwise calcium-deficient diet (127). Changes in nerve and muscle irritability have been studied by chronaximetric measurements in animals receiving an acidotic rachitogenic diet (128). Such a diet is apt to inhibit vitamin D synthesis produced by ultraviolet rays (129).

*Fluorine.*—Whereas there have been many reports concerning the protective influence of fluorine on tooth enamel, only a few deal with its action on bone. The enzymatic and protoplasmic action of fluorine promotes rickets-like changes in the bones of puppies, but its effect on the bones of older dogs is different from rickets (130). Besides, sodium fluoride does not affect the calcemia

or phosphoremia of normal rats unless the diet is not properly balanced (131). In a review dealing with the biological importance of phosphomonoesterase (42), it has been recalled that fluorine reduces the accumulation in bone of the glycogen related to the production of phosphoric esters.

*Vitamin A.*—The action of vitamin A on bone is exerted through the osteoblasts (132); its deficiency produces an accelerated remodeling of bone and a laying down of defective tissue (133). The activity of the osteoclasts is also affected. The disturbances are reversible if the vitamin A deficiency is corrected (134). Hypervitaminosis A has some action on bone growth (135). A study of its clinical features (136) has been published.

*Vitamin B.*—Deficiency in riboflavin leads to slowing of chondrogenesis and endochondreal ossification in rats (137). Those phenomena, which have been shown in mice to be reversible (138), are also produced by deficiency in total vitamin B complex (139), pantothenic acid (140), and pyridoxine; in this last case, the disturbances are accentuated by excess dietary proteins (141).

*Vitamin C.*—Growth of the odontoblasts in the rat's incisors is directly related to the vitamin C content of the diet (142). It has been emphasized that vitamin C is necessary for tooth growth (143). Its importance in fracture repair and ossification has been reviewed (144). With partial vitamin C deficiency, compact bone becomes porotic, but this is often accompanied by hyperostosis: the callus of fractured bone fails to become compact and retains trabecular structure (145).

*Vitamin D.*—The fundamental process of ossification in rachitic rats is only slightly abnormal, the reduced strength of rachitic bone being due solely to insufficient mineralization (146). Rickets lesions are often accompanied by osteopetrosis (147). Histological and histochemical methods have been applied to the detection of the early signs of avitaminosis D and the quantitative determination of bone phosphatase (148, 149). Rickets also produces some changes in the ionic product of serum calcium phosphates (150).

The mode of action and the therapeutic indications of vitamin D have been reviewed (151, 152). It has been said to act essentially by preventing the solution of bone calcium (153). The influence of vitamin D on calcium balance is very different in normal individuals and in subjects suffering from rickets or other bone disease (154, 155, 156).

Studies were devoted to the action of vitamin D on different types of rickets: rickets due to an unbalanced Ca/P ratio in the diet (123), to liver disturbances (157), and to excess mineral sulfates in drinking water (158). Rickets produced by a diet with a high Ca/P ratio is cured by a normal diet, but the curative action is different from that exhibited by vitamin D (159) or citric acid (160). In South Africa, summer sunshine provides full protection against rickets; its action has been estimated equivalent to 2,500 I.U. a day (161).

The widely accepted opinion that vitamin D is stored in the liver has been criticized (162).

A detailed critical study of the chicken assay for vitamin D has been made (163 to 169); the line test and the chemical methods have been compared (170). A rachitogenic index representing the rachitogenic value of the diet has been defined (171).

As it has been emphasized again in many publications, hypervitaminosis D produces metastatic calcifications especially in the lungs, the myocardium, the kidneys, and the gastric mucosa. Abnormal calcification can occur either after one high dose of vitamin D or after repeated and prolonged administration (172 to 178). Hypervitaminosis D also causes atrophy of the parathyroids (175). Hypercalcemia cannot be considered as a toxicity test for vitamin D (179).

#### INFLUENCE OF HORMONAL FACTORS ON BONE

The influence of hormones on osteogenesis in man has been detailed in Albright's extensive report (180).

*Adrenals.*—It has been confirmed that adrenocorticotrophic hormone retards chondro- and osteogenesis (181).

*Hypophysis.*—The role of the pituitary growth hormone has been recently reviewed (182). Hypophysectomy is followed by acceleration of ossification and senescence of the mandibular joint (183), but stops chondrogenesis and osteogenesis in the third metacarpal (184). The hormone restores growth processes in the senescent mandibular joint (185) and in the epiphyseal cartilage plate of the third metacarpal of hypophysectomized rats (186). In normal rats, it prolongs the period of growth especially at the mandibular condyle (187), to a smaller extent at the tibia and at the costo-chondral junction (188), but not at all at the third metacarpal (189).

*Thyroid.*—Thyroidectomy transitorily retards the ossification of the mandibular joint (190), the tibia, the metacarpals, and the caudal vertebrae (191). In hypophysectomized rats, thyroxine failed to reactivate growth at the mandibular joint and at the third metacarpal; moreover, it inhibited the response to the growth hormone (185, 186). Thyroxine enhances the formation of the organic bone matrix (192).

*Parathyroids.*—From some studies devoted to the relations between parathyroids and mineral metabolism, it has been concluded that parathormone influences through the kidney the metabolism of phosphorus (193) and, secondarily, of calcium and strontium (194). The hypercalcemia due to injections of parathyroid extracts is said to be directly related to their diuretic effects (195). Increased diuresis is accompanied by an increased renal blood flow; the responsible pressor substance might not be the hormone which mobilizes calcium (196). Urinary variations of phosphate concentration seem to be parallel to those of glucose (197). Parathyroid extract has been said to have a direct action on bone (198). In young dogs, prolonged administration modifies the composition of bones more than dietary mineral variations are able to (199). The relations between hyperparathyroidism and decalcification of the skeleton have been reviewed (200). Studies were devoted to the pathogenesis of the clinical manifestations of hyperparathyroidism (201). Nephrectomy or ligation of the ureters is soon followed by hypertrophy and hyperplasia of the parathyroids; the histological features of the glandular cells in such cases have been described and discussed (202). Parathyroid hypertrophy can be produced by renal lesions (203), liver disturbances (204), and low Ca/P ratio in the diet (205). It has been shown in dogs that renal lesions can be followed by osteofibrosis (206). The relations between parathyroids and the skeleton in kidney disease have been dealt with in Gilmour's recent monograph (207). Parathyroid activity partially depends upon the anterior pituitary body (208).

It seemed that the existence of a functional equilibrium between parathyroid secretion and vitamin D has been clearly established by Studitskii (209), who has shown in chick embryos that anterior pituitary grafts into the chorio-allantois are frequently followed by chondro-dystrophy; the mechanism of this effect would be a stimulation of the parathyroids. However, these conclusions have been criticized by Landauer (210); in the chick, the

causes for the abnormal bone evolution exist long before the embryonal development of the endocrines.

*Sexual hormones.*—Injection of estradiol benzoate to chick embryos does not induce hypercalcification of the femur (211) as it does in adults. Endosteal osteogenesis requires constant administration of estrogen. In parathyroidectomized ducks receiving folliculin, medullar ossein trabeculae are formed normally, but their calcification is prevented (212). The action of folliculin is local as it is present after injection into a long bone (213). In ducks receiving a calcium-deficient diet together with injections of folliculin, ossein trabeculae develop, but there is only a partial calcification at the expense of the mineral reserves in bone (214). These purely organic trabeculae do not attract osteoclasts (215). Blood depletion is followed by medullary hyperplasia and increases bone response to estrogen (216). The osteoblasts have an important role in endosteal osteogenesis: they derive from the medullar reticulum and their activity is maintained by folliculin. When folliculin administration is discontinued, the osteoblasts become osteoclasts and destroy the trabeculae (217).

Estrogen can cause hypomineralization, which is a consequence of abnormal formation of the proteinic matrix by the osteoblasts (218). The Ca/P ratio in recently built trabeculae is higher than in normal bone. These trabeculae have been said to contain apatite and calcium carbonate in an irregular crystalline mixture; the same condition would occur in the femoral cortex under the influence of folliculin (219). However, the principal constituent of new bone is tricalcium phosphate, as can be shown by chemical analysis, determination of refractive indices, and study of x-ray diffraction spectra (220).

Part of the phosphorus present in endosteal bone is provided by the skeleton, as has been shown in pigeons receiving a normal amount of dietary phosphorus supplemented by injected radiophosphorus (221). The same procedure has shown that the exchanges of phosphorus are significantly accelerated by folliculin; this happens in all bones, especially those undergoing endosteal osteogenesis (222). Only the bones of this latter group, however show accelerated calcium exchanges under the influence of estrogen, as has been demonstrated by a parallel study using radiocalcium. In other bones, for instance the humerus, bone calcium metabolism is not different from the controls receiving no folliculin.

Furthermore, folliculin has been said to influence the intestinal resorption of calcium (223). Estrogen has no influence on the bones of puppies (224); its action on bone absorption and relaxation of pelvis has been studied in guinea pigs (225).

In pigeons androgen is necessary to the action of folliculin on bone; in sparrows, only age and seasonal factors seem to have a role (226). Dietary restrictions associated with administration of sesame oil induce bone atrophy in limbs either normal or paralyzed by nervous section; this effect is minimized by estrogen (125). While the male sexual hormone is rachitogenic, folliculin has the opposite effect; alone, or associated with vitamin D, it is apt to antagonize hyperparathyroidism (227). Castration retards growth by inhibiting the hypertrophic development of cartilaginous cells (228); this effect is antagonized by thyroxine which stimulates this hypertrophy (229). In ducks, thyroidectomy slows the formation of the proteinic trabeculae; and even though there is a slower rise in calcemia under the influence of folliculin (230), calcification of endosteal bone is more active (231). These results emphasize the general stimulating action of thyroxine on tissue metabolism as well as its property of increasing calcium excretion. While thyroxine apparently does not inhibit estrogen action on endosteal osteogenesis, it reduces the rise in calcemia following administration of folliculin (232).

In growing mice, the effects of estrogen given together with thyroxine are altered: each hormone predominates during the stage where its action would have been most intense if it had been injected alone (233). In impuberal rats, natural as well as synthetic estrogens produce a narrowing of the epiphyseal lines followed by hyperossification. These changes do not occur in adult rats (234). The estrogen-induced formation of endosteal bone in rats requires the presence of the pituitary body, but not of the parathyroids. The amount of bony trabeculae is increased because estrogen makes bone resorption deficient (235).

In growing guinea pigs suffering from avitaminosis C, estrogen administration is unable to induce the evolution of the proteinic matrix into bone; however, the appearance of scurvy lesions is prevented in these animals as well as in adults (236). Estrogen does not alter the metabolism of ascorbic acid (237).

The physiology of antlers is an interesting problem related to the sexual glands; it has been mentioned in many biological

reviews (238, 239). Thorough studies have been devoted to the seasonal changes affecting antlers (240, 241, 242).

## LITERATURE CITED

1. MURRAY, P. D. F., *Ann. Rev. Physiol.*, **9**, 103 (1947)
2. WEINMANN, J. P., AND SICHER, H., *Bone and Bones—Fundamentals of Bone Biology*, 464 pp. (Kimpton, London, 1947)
3. LACROIX, P., *L'Organisation des os*, 230 pp. (Desoer, Liège, 1949)
4. LEICESTER, H. M., *Biochemistry of the Teeth*, 306 pp. (Mosby, St. Louis, 1949)
5. MAYNARD, L. A., AND SMITH, S. E., *Ann. Rev. Biochem.*, **16**, 273 (1947)
6. AMPRINO, R., AND GODINA, G., *Commentationes Pontificia Acad. Sci.*, **11**, 329 (1947)
7. AMPRINO, R., AND GODINA, G., *Atti accad. nazl. Lincei, Classe sci. fis. mat. e nat.*, **1**, 648 (1946)
8. AMPRINO, R., *Arch. biol. (Liège)*, **58**, 315 (1947)
9. AMPRINO, R., *Arch. sci. biol. (Italy)*, **31**, 208 (1946)
10. GODINA, G., *Arch. ital. anat. embriol.*, **52**, 161 (1947)
11. AMPRINO, R., *Acta Anat.*, **5**, 291 (1948)
12. BECKS, H., ASLING, C. W., SIMPSON, M. E., EVANS, A. M., AND LI, C. H., *Am. J. Anat.*, **82**, 203 (1948)
13. COLLINS, D. A., BECKS, H., SIMPSON, M. E., AND EVANS, H. M., *Am. J. Orthodontics Oral Surg.*, **32**, 431 (1946)
14. BECKS, H., ASLING, C. W., COLLINS, D. A., SIMPSON, M. E., AND EVANS, H. M., *Anat. Rec.*, **100**, 577 (1948)
15. RUTH, E. B., *Anat. Rec.*, **98**, 59 (1947)
16. RUTH, E. B., *Am. J. Anat.*, **80**, 35 (1947)
17. LAMAS, A., AMADO, D., AND CELESTINO DACOSTA, J., *Presse méd.*, **54**, 862 (1946)
18. DALLEMAGNE, M. J., AND MELON, J., *J. Wash. Acad. Sci.*, **36**, 181 (1946)
19. ASCENZI, A., *Atti accad. nazl. Lincei, Classe sci. fis. mat. e nat.*, **5**, 171 (1948)
20. ASCENZI, A., *Atti accad. nazl. Lincei, Classe sci. fis. mat. e nat.*, **5**, 100 (1948)
21. BAUD, C. A., AND DALLEMAGNE, M. J., *Science*, **110**, 90 (1949)
22. ASCENZI, A., *Nature*, **163**, 604 (1949)
23. DALLEMAGNE, M. J., AND MELON, J., *Compt. rend. soc. biol.*, **141**, 539 (1947)
24. ASCENZI, A., *Atti accad. nazl. Lincei, Classe sci. fis. mat. e nat.*, **4**, 777 (1948)
25. HANCOX, N. M., *J. Physiol. (London)*, **106**, 279 (1947)
26. HANCOX, N. M., *J. Physiol. (London)*, **107**, 513 (1948)
27. HANCOX, N. M., *J. Physiol. (London)*, **105**, 66 (1946)
28. LACROIX, P., *Arch. biol. (Liège)*, **59**, 391 (1948)
29. LACROIX, P., *Arch. biol. (Liège)*, **59**, 379 (1948)
30. VINCENT, J., *Bull. histol. appl. à physiol. et path. et tech. microscop.*, **25**, 180 (1948)
31. PAFF, G. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 288 (1948)
32. WILLSTAEDT, H., LEVANDER, G., AND HULT, L. (Personal communication, 1949)
33. LEVANDER, G., *Acta Path. Microbiol. Scand.*, **26**, 113 (1949)
34. LACROIX, P., *Arch. biol. (Liège)*, **57**, 99 (1946)
35. LACROIX, P., *Bull. acad. roy. méd. Belg.*, **10**, 517 (1945)

36. LACROIX, P., *J. Bone Joint Surg.*, **29**, 292 (1947)
37. LACROIX, P., *Arch. biol. (Liège)*, **60**, 1 (1949)
38. TEUCQ, E., *Arch. biol. (Liège)*, **59**, 1 (1948)
39. LACROIX, P., *Arch. biol. (Liège)*, **60**, 14 (1949)
40. PFEIFFER, C. A., *Anat. Rec.*, **102**, 225 (1948)
41. ROCHE, J., *Experientia*, **2**, 325 (1946)
42. MOOG, F., *Biol. Revs. Cambridge Phil. Soc.*, **21**, 41 (1946)
43. GLOCK, G. E., *J. Physiol. (London)*, **98**, 1 (1940)
44. GUTMAN, A. B., AND GUTMAN, E. B., *Proc. Soc. Exptl. Biol. Med.*, **48**, 687 (1931)
45. GUTMAN, A. B., WARRICK, F. B., AND GUTMAN, E. B., *Science*, **95**, 461 (1942)
46. ROCHE, J., in *Actualités Biochimiques*, 10 (Desoer, Liège, 1947)
47. LORCH, I. J., *J. Bone Joint Surg. [B]*, **31**, 94 (1949)
48. DALLEMAGNE, M. J., *Nature*, **161**, 115 (1948)
49. MELON, J., AND DALLEMAGNE, M. J., *Bull. soc. chim. Belges.*, **55**, 38 (1946)
50. MELON, J., AND DALLEMAGNE, M. J., *Bull. soc. chim. Belges.*, **56**, 180 (1947)
51. DALLEMAGNE, M. J., *Acta physiother. Rheumatol. Belgica*, **3**, 77 (1947)
52. BENESCH, R., CHANCE, M. R. A., AND GLYNN, L. E., *Nature*, **155**, 203 (1945)
53. MILLER, Z. B., WALDMAN, J., AND MCLEAN, F. C., *Nature*, **161**, 272 (1948)
54. GREENWALD, I., *J. Biol. Chem.*, **161**, 697 (1945)
55. DALLEMAGNE, M. J., AND MELON, J., *Bull. soc. chim. biol.*, **28**, 566 (1946)
56. MONNIER, A. M., BONNET, V., AND BRARD, R., *Arch. intern. physiol.*, **54**, 188 (1946)
57. MONNIER, A. M., AND BONNET, V., *Arch. sci. physiol.*, **1**, 91 (1947)
58. JOSEPH, N. R., *J. Biol. Chem.*, **164**, 29 (1946)
59. CAPPELLIN, M., *Mon. zool. ital.*, **56**, 256 (1948)
60. LORCH, I. J., *Nature*, **158**, 269 (1946)
61. BARGER, J. D., *Arch. Path.*, **43**, 620 (1947)
62. DANIELLI, J. F., *J. Exptl. Biol.*, **22**, 110 (1946)
63. LORCH, I. J., *Quart. J. Microscop. Sci.*, **88**, 367 (1947)
64. LORCH, I. J., *Quart. J. Microscop. Sci.* (In press)
65. GREEP, R. O., FISCHER, C. J., AND MORSE, A., *J. Am. Dental Assoc.*, **36**, 427 (1948)
66. NGUYEN-VAN THOAI, ROCHE J., AND ROGER, M., *Biochem. et Biophys. Acta*, **1**, 61 (1947)
67. CAPPELLIN, M., *Sperimentale*, **99**, 133 (1948)
68. WISLOCKI, G. B., AND DEMPSEY, E. W., *Am. J. Anat.*, **76**, 277 (1945)
69. ROCHE, J., in *Biochemische Actualiteiten* (Vlaamse Chemische Vereniging, Antwerpen, 1947)
70. CAPPELLIN, M., *Boll. soc. ital. biol. sper.*, **24**, 1228 (1948)
71. CAPPELLIN, M., *Atti soc. med. chir. Padova*, **25**, 86 (1947)
72. CAPPELLIN, M., *Rass. Biol. Um.*, **3**, 35 (1948)
73. MCKELVIE, A. M., AND MANN, F. C., *Proc. Staff Meetings Mayo Clinic*, **23**, 449 (1948)
74. JOHNSON, P. L., BUTCHER, E. O., AND BEVELANDER, G., *Anat. Record*, **93**, 355 (1945)
75. BEVELANDER, G., AND JOHNSON, P. L., *J. Cellular Comp. Physiol.*, **28**, 129 (1946)

76. BEVELANDER, G., AND BENZER, P., *Biol. Bull.*, **94**, 176 (1948)
77. SLESSOR, A., AND WYBURN, G. M., *Lancet.*, **I**, 212 (1948)
78. SILVER, P. H., AND GOLDING, J. S. R., *Lancet*, **I**, 528 (1945)
79. BOURNE, G. H., *J. Anat.*, **82**, 81 (1948)
80. BODANSKY, O., *Federation Proc.*, **8**, 185 (1949)
81. LOMBARD, P., VERAINE, ROYER, AND COUILLAUD, *Mem. acad. chir.*, **71**, 180 (1945)
82. BEVERS, C. A., *Brit. Sci. News*, **1**, 4 (1947)
83. BEVERS, C. A., AND MCINTYRE, D. B., *Mineralog. Mag.*, **27**, 254 (1946)
84. BRASSEUR, H., DALLEMAGNE, M. J., AND MELON, J., *Nature*, **157**, 453 (1946)
85. DALLEMAGNE, M. J., AND BRASSEUR, H., *Experientia*, **3**, 469 (1947)
86. MCINTYRE, W. H., PALMER, G., AND MARCHALL, H. L., *Ind. Eng. Chem.*, **37**, 164 (1945)
87. BRANDENBERGER, E., AND SCHINZ, H. R., *Experientia*, **4**, 59 (1948)
88. BRASSEUR, H., DALLEMAGNE, M. J., AND MELON, J., *Experientia*, **3**, 421 (1948)
89. DALLEMAGNE, M. J., BRASSEUR, H., AND MELON, J., *Bull. soc. chim. France*, **D**, 138 (1949)
90. DALLEMAGNE, M. J., BRASSEUR, H., AND MELON, J., *Bull. soc. chim. biol.*, **31**, 425 (1949)
91. CARTIER, P., *Bull. Soc. chim. biol.*, **30**, 65 (1948)
92. BRASSEUR, H., AND DALLEMAGNE, M. J., *Bull. soc. chim. France*, **D**, 135 (1949)
93. DAWSON, I. M., *Nature*, **157**, 660 (1946)
94. HENNY, G. C., AND SPIEGEL-ADOLPH, M., *Am. J. Physiol.*, **144**, 632 (1945)
95. THUNBERG, T., *Acta Physiol. Scand.*, **14**, 245 (1947)
96. THUNBERG, T., *Acta Physiol. Scand.*, **15**, 38 (1948)
97. CARTIER, P., *Bull. soc. chim. biol.*, **30**, 73 (1948)
98. POLONOWSKI, M., AND CARTIER, P., *Bull. soc. chim. biol.*, **28**, 247 (1946)
99. CARTIER, P., *Bull. soc. chim. biol.*, **28**, 273 (1946)
100. CARTIER, P., *Bull. soc. chim. biol.*, **28**, 258 (1946)
101. SACKS, J., *Chemical Rev.*, **42**, 411 (1948)
102. DOUGHERTY, E. C., AND LAWRENCE, J. H., *Calif. Med.*, **69**, 1 (1948)
103. HEVESY, G., *Radioactive isotopes*, 556 pp. (Interscience, New York 1948)
104. FALKENHEIM, M., NEUMAN, W. F., AND HODGE, H. C., *J. Biol. Chem.*, **169**, 713 (1947)
105. NEUMAN, W. F., AND RILEY, R. F., *J. Biol. Chem.*, **168**, 585 (1947)
106. RILEY, R. F., MCCLEARY, B., AND JOHNSON, R. E., *Am. J. Physiol.*, **143**, 677 (1945)
107. ARMSTRONG, W. D., *Federation Proc.*, **6**, 235 (1947)
108. ARMSTRONG, W. D., AND BARNUM, C. P., *J. Biol. Chem.*, **172**, 199 (1948)
109. COPP, D. H., AXELROD, D. J., AND HAMILTON, J. G., *Am. J. Roentgen. Radium Therapy*, **58**, 10 (1947)
110. NEUMAN, W. F., NEUMAN, M. W., AND MULRYAN, B. J., *J. Biol. Chem.*, **175**, 705 (1948)
111. O'NEIL, J. B., JOWSEY, J. R., LEE, C. C., READE, M. A., AND SPINKS, J. W. T. *Science*, **107**, 295 (1948)

112. COMAR, C. L., AND DRIGGERS, J. C., *Science*, **109**, 282 (1949)
113. HARRISON, H. E., AND HARRISON, H. C., *Federation Proc.*, **8**, 68 (1949)
114. REED, J. C., AND JONES, H. B., *J. Biol. Chem.*, **174**, 427 (1948)
115. TOBIAS, C. A., AND DUNN, R. W., *Science*, **109**, 109 (1949)
116. ARMSTRONG, W. D., SCHUBERT, J., AND LINDENBAUM, A., *Proc. Soc. Exptl. Biol. Med.*, **68**, 233 (1948)
117. DELLUVA, A. N., AND WILSON, D. W., *J. Biol. Chem.*, **166**, 739 (1946)
118. MULLENS, L. J., AND ZERAHN, K., *J. Biol. Chem.*, **174**, 107 (1948)
119. SAXTON, J. A., AND SILBERBERG, N., *Am. J. Anat.*, **81**, 445 (1947)
120. ESTREMER, H. R., AND ARMSTRONG, W. D., *J. Nutrition*, **35**, 611 (1948)
121. DUTTA, N. C., *Ann. Biochem. Exptl. Med. (India)*, **8**, 69 (1948)
122. HOLTZ, F., POPPER, H., AND SILBERMANN, L., *Biochem. Z.*, **318**, 149 (1947)
123. MIGICOVSKY, B. B., AND EMSLIE, A. R. G., *Arch. Biochem.*, **13**, 175 (1947)
124. IRVING, J. T., *J. Physiol. (London)*, **105**, 16 (1946)
125. ARMSTRONG, W. D., *J. Nutrition*, **35**, 597 (1948)
126. HIRSCHMAN, A., SOBEL, A. E., KRAMER, B., AND FANKUCHEN, I., *J. Biol. Chem.*, **171**, 285 (1947)
127. CROSNIER, R., GIRARD, P., RENAULT, J., AND GROUSSAULT, S., *J. Physiol. et path. gén.*, **39**, 331 (1947)
128. LECOQ, R., CHAUCHARD, P., AND MAZOUÉ, H., *Thérapie*, **2**, 272 (1947)
129. LECOQ, R., *Thérapie*, **2**, 73 (1947)
130. BAUER, W. H., *Am. J. Orthodontics Oral Surg.*, **31**, 700 (1945)
131. IRVING, J. I., AND NIENABER, M. W. P., *J. Dental Research*, **25**, 327 (1946)
132. IRVING, J. I., *Nature*, **162**, 377 (1948)
133. WOLBACH, S. B., *Proc. Inst. Med. Chicago*, **16**, 188 (1946)
134. MELLANBY, E., *J. Physiol. (London)*, **105**, 382 (1947)
135. VAN METRE, T. E., JR., *Bull. Johns Hopkins*, **81**, 305 (1947)
136. TOOMEY, J. A., AND MORISSETTE, R. A., *Am. J. Diseases Children*, **73**, 473 (1947)
137. NELSON, M. M., SULON, E., BECKS, H., AND EVANS, H. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 631 (1947)
138. LEVY, B. M., AND SILBERBERG, R., *Proc. Soc. Exptl. Biol. Med.*, **63**, 355 (1946)
139. SILBERBERG, M., LEVY, B. M., AND YOUNGER, F., *Proc. Soc. Exptl. Biol. Med.*, **67**, 185 (1948)
140. LEVY, B. M., AND SILBERBERG, R., *Proc. Soc. Exptl. Biol. Med.*, **63**, 380 (1946)
141. SILBERBERG, R., AND LEVY, B. M., *Proc. Soc. Exptl. Biol. Med.*, **67**, 259 (1948)
142. CRAMPTON, E. W., *J. Nutrition*, **33**, 491 (1947)
143. GIROUD, A., AND PARANT, M., *Rev. stomatol.*, **48**, 44 (1947)
144. BOURNE, G. H., *Proc. Nutrition Soc. (Engl. and Scot.)*, **4**, 204 (1946)
145. MURRAY, P. D. F., AND KODICEK, E., *Proc. Nutrition Soc. (Engl. and Scot.)*, **4**, 200 (1946)
146. BELL, G. H., CHAMBERS, J. W., AND DAWSON, I. M., *J. Physiol. (London)*, **106**, 286 (1947)
147. PINCUS, J. B., GITTLEMAN, I. F., AND KRAMER, B., *Am. J. Diseases Children*, **73**, 458 (1947)
148. LECOQ, R., AND CHAMPEAU, M. F., *Compt. rend. soc. biol.*, **141**, 995 (1947)

149. CHAMPEAU, M. F., AND LECOQ, R., *Compt. rend. soc. biol.*, **141**, 993 (1947)
150. DIKSHIT, P. K., AND PATWARDHAN, V. N., *Indian J. Med. Research*, **34**, 263 (1946)
151. MACH, R. S., in *3e journée de thérapeutique clinique* (A. Skira, Genève, 1947)
152. VOLLMER, H., AND OSER, B. L., *J. Pediat.*, **30**, 446 (1947)
153. MIGICOVSKY, B. B., AND EMSLIE, A. R. G., *Arch. Biochem.*, **20**, 325 (1949)
154. MACH, R. S., FABRE, J., AND DELLA SANTA, R., *J. suisse med.*, **78**, 453 (1948)
155. HOUEY, R., *Ann. Paediat.*, **167**, 127 (1946)
156. HOUEY, R., *Ann. Paediat.*, **166**, 177 (1946)
157. HOUEY, R., *Ann. Paediat.*, **167**, 113 (1946)
158. GLANZMANN, E., MEIER, K., AND UEHLINGER, E., *Z. Vitaminforsch.*, **17**, 130 (1946)
159. IRVING, J. I., *J. Physiol. (London)*, **104**, 253 (1946)
160. GLANZMANN, E., MEIER, K., AND WALTHARD, B., *Z. Vitaminforsch.*, **17**, 159 (1946)
161. IRVING, J. I., AND SCHWARTZ, H. M., *Clin. Proc. (Cape Town)*, **4**, 260 (1945)
162. HOUEY, R., *Ann. Paediat.*, **166**, 169 (1946)
163. CAMPBELL, J. A., AND EMSLIE, A. R. G., *Poultry Sci.*, **26**, 255 (1947)
164. CAMPBELL, J. A., AND EMSLIE, A. R. G., *Poultry Sci.*, **24**, 296 (1945)
165. CAMPBELL, J. A., AND EMSLIE, A. R. G., *Poultry Sci.*, **24**, 201 (1945)
166. CAMPBELL, J. A., AND EMSLIE, A. R. G., *Poultry Sci.*, **26**, 568 (1947)
167. CAMPBELL, J. A., AND EMSLIE, A. R. G., *Poultry Sci.*, **26**, 573 (1947)
168. CAMPBELL, J. A., MIGICOVSKY, B. B., AND EMSLIE, A. R. G., *Poultry Sci.*, **24**, 3 (1945)
169. CAMPBELL, J. A., MIGICOVSKY, B. B., AND EMSLIE, A. R. G., *Poultry Sci.*, **24**, 72 (1945)
170. BILLS, C. E., *Biol. Symposia*, **12**, 409 (1947)
171. MIGICOVSKY, B. B., AND EMSLIE, A. R. G., *Arch. Biochem.*, **13**, 185 (1947)
172. MORGAN, A. F., AXELROD, H. E., AND GROODY, M., *Am. J. Physiol.*, **149**, 333 (1947)
173. HENDRICKS, J. B., MORGAN, A. F., AND FREYTAG, R. M., *Am. J. Physiol.*, **149**, 319 (1947)
174. MULLIGAN, R. M., *Am. J. Path.*, **22**, 1293 (1946)
175. MULLIGAN, R. M., AND STRICKER, F. L., *Am. J. Path.*, **24**, 451 (1948)
176. FROST, J. W., SUNDERMAN, F. W., AND LEOPOLD, I. H., *Am. J. Med. Sci.*, **214**, 639 (1947)
177. KAUFMAN, P., BECK, R. D., AND WISEMAN, R. D., *J. Am. Med. Assoc.*, **134**, 688 (1947)
178. MACH, R. S., AND DUCOMMUN, P., *J. suisse med.*, **78**, 732 (1948)
179. REED, C. I., *Federation Proc.*, **6**, 185 (1947)
180. ALBRIGHT, F., *Recent Progress Hormone Research*, **1**, 293 (1947)
181. BAKER, B. L., AND INGLE, D. J., *Endocrinology*, **43**, 422 (1948)
182. FØNSS-BECH, P., *Acta Pharmacol. Toxicol.*, **3**, Suppl. 3 (1947)
183. COLLINS, D. A., BECKS, H., SIMPSON, M. E., AND EVANS, H. M., *Am. J. Orthodontics Oral Surg.*, **32**, 443 (1946)
184. COLLINS, D. A., BECKS, H., ASLING, C. W., SIMPSON, M. E., AND EVANS, H. M., *Anat. Record*, **101**, 13 (1948)
185. COLLINS, D. A., BECKS, H., SIMPSON, M. E., AND EVANS, H. M., *Am. J. Orthodontics Oral Surg.*, **32**, 447 (1946)

186. BECKS, H., ASLING, C. W., COLLINS, D. A., SIMPSON, M. E., LI, C. H., AND EVANS, H. M., *Anat. Record*, **101**, 17 (1948)
187. BECKS, H., COLLINS, D. A., ASLING, C. W., SIMPSON, M. E., LI, C. H., AND EVANS, H. M., *Growth*, **12**, 55 (1948)
188. EVANS, H. M., BECKS, H., ASLING, C. W., SIMPSON, M. E., AND LI, C. H., *Growth*, **12**, 43 (1948)
189. ASLING, C. W., BECKS, H., SIMPSON, M. E., LI, C. H., AND EVANS, H. M., *Anat. Record*, **101**, 23 (1948)
190. BECKS, H., COLLINS, D. A., ASLING, C. W., SCOW, R. O., SIMPSON, M. E., AND EVANS, H. M., *Oral Surg. Med. Path.*, **1**, 315 (1948)
191. BECKS, H., SIMPSON, M. E., SCOW, R. O., ASLING, C. W., AND EVANS, H. M., *Anat. Record*, **100**, 561 (1948)
192. BENOIT, J., AND CLAVERT, J., *Arch. Anat. Micro. Morph. Exptl.*, **37**, 214 (1948)
193. TWEEDY, W. R., CHILCOTT, M. E., AND PATRAS, M. C., *J. Biol. Chem.*, **168**, 597 (1947)
194. TWEEDY, W. R., *J. Biol. Chem.*, **161**, 105 (1945)
195. MOEHLIG, R. C., AND ABBOTT, H. L., *J. Michigan State Med. Soc.*, **46**, 1397 (1947)
196. HANDLER, P., AND DE MARIA, W. J. A., *Federation Proc.*, **8**, 204 (1949)
197. CARGILL, W. H., AND WITHAM, A. C., *Federation Proc.*, **8**, 21 (1949)
198. MCCHESENEY, E. W., AND GIACOMINO, N. J., *J. Clin. Invest.*, **24**, 680 (1945)
199. BURNS, C. M., AND HENDERSON, N., *Biochem. J.*, **40**, 501 (1946)
200. MASMONTEIL, F., LEURET, J., AND CARTIER, P., *Rev. Orthop.*, **34**, 120 (1948)
201. STEPHENSON, H. V., AND McNAMARA, W. J., *Am. J. Med. Sci.*, **215**, 381 (1948)
202. BAKER, B. L., *Anat. Record*, **93**, 125 (1945)
203. LIEGEOIS, F., AND DERIVAUX, J., *Compt. rend. soc. biol.*, **140**, 1143 (1946)
204. MULLIGAN, R. M., *Arch. Path.*, **40**, 182 (1945)
205. LIEGEOIS, F., AND DERIVAUX, J., *Compt. rend. soc. biol.*, **143**, 128 (1949)
206. LIEGEOIS, F., AND DERIVAUX, J., *Rev. path. comp.*, **46**, 486 (1946)
207. GILMOUR, J. R., *The Parathyroid Glands and Skeleton in Renal Disease*, 157 pp. (Oxford Medical Publications, London, 1947)
208. BENOIT, J., AND CLAVERT, J., *Acta Anat.*, **4**, 49-1947)
209. STUDITSKII, A. N., *Nature*, **157**, 427 (1946)
210. LANDAUER, W., *Nature*, **157**, 838 (1946)
211. GABRIO, B. W., AND SALOMON, K., *Endocrinology*, **42**, 73-76 (1948)
212. BENOIT, J., AND CLAVERT, J., *Compt. rend. ass. anat.*, **50**, 2734 (1947)
213. BENOIT, J., AND CLAVERT, J., *Compt. rend. soc. biol.*, **139**, 728 (1945)
214. BENOIT, J., AND CLAVERT, J., *Compt. rend. soc. biol.*, **139**, 737 (1945)
215. BENOIT, J., AND CLAVERT, J., *Compt. rend. soc. biol.*, **141**, 911 (1947)
216. SALOMON, K., GABRIO, B. W., REINHARD, E., AND SILBERBERG, R., *Arch. Path.*, **43**, 76 (1947)
217. CLAVERT, J., *Arch. Anat. Micro. Morph. Exptl.*, **37**, 41 (1948)
218. REIFENSTEIN, E. C., AND ALBRIGHT, F., *J. Clin. Invest.*, **26**, 24 (1947)
219. REED, C. I., REED, B. P., AND GARDNER, W. U., *Endocrinology*, **38**, 238 (1946)
220. DALLEMAGNE, M. J., AND MELON, J., *Compt. rend. soc. biol.*, **141**, 539 (1947)
221. DALLEMAGNE, M. J., GOVAERTS, J., AND SUE, P., *Compt. rend. soc. biol.*, **141**, 541 (1947)

- 222. GOVAERTS, J., AND DALLEMAGNE, M. J., *Nature*, **161**, 977 (1948)
- 223. DALLEMAGNE, M. J., GOVAERTS, J., AND MELON, J., *Experientia*, **5**, 331 (1949)
- 224. BAUER, W. H., *J. Am. Coll. Dentists*, **12**, 192 (1945)
- 225. YOUNG, W. C., AND EMERY, F. E., *Federation Proc.*, **8**, 174 (1949)
- 226. PFEIFFER, C. A., *Anat. Record*, **94**, 362 (1946)
- 227. NORMAN, G. F., AND MITTLER, A., *Proc. Soc. Exp. Biol. Med.*, **67**, 104 (1948)
- 228. SILBERBERG, M., AND SILBERBERG, R., *Anat. Record*, **95**, 97 (1946)
- 229. SILBERBERG, M., AND SILBERBERG, R., *Anat. Record*, **98**, 181 (1947)
- 230. BENOIT, J., AND CLAVERT, J., *Compt. rend soc. biol.*, **141**, 1256 (1947)
- 231. BENOIT, J., AND CLAVERT, J., *Arch. Anat. Micro. Morph. Exptl.*, **37**, 214 (1948)
- 232. MC DONALD, M. R., RIDDLE, O., AND SMITH, G. C., *Endocrinology*, **37**, 23 (1945)
- 233. SILBERBERG, M., AND SILBERBERG, R., *Am. J. Path.*, **22**, 1033 (1946)
- 234. PINDBORG, J. J., *Acta Path. Microbiol. Scand.*, **22**, 290 (1945)
- 235. BAKER, B. L., AND LEEK, J. H., *Am. J. Physiol.*, **147**, 522 (1946)
- 236. SILBERBERG, M., AND SILBERBERG, R., *Am. J. Path.*, **24**, 1019 (1948)
- 237. SILBERBERG, M., AND SILBERBERG, R., *Anat. Record*, **102**, 141-160 (1948)
- 238. THOMSON, J. A., *Science Old and New*, 192 pp. (Melrose, London, 1946)
- 239. BEACH, F. A., *Hormones and Behaviour*, 368 pp. (Hoeber, New York, 1948)
- 240. WISLOCKI, G. B., AND SINGER, M., *J. Comp. Neur.*, **85**, 1 (1946)
- 241. WISLOCKI, G. B., AUB, J. C., AND WALDO, C. M., *Endocrinology*, **40**, 202 (1947)
- 242. WISLOCKI, G. B., WEATHERFORD, H. I., AND SINGER, M., *Anat. Record*, **99**, 265 (1947)

## PHYSIOLOGICAL RESPONSES TO HEAT AND COLD

BY JAMES D. HARDY

*The Russell Sage Institute of Pathology, affiliated with The New York Hospital,  
The Department of Physiology, Cornell University Medical College,  
New York, N. Y.*

### INTRODUCTION

The practical interests of the military agencies in the problems of heat and cold tolerance of men has kept alive much of the research in this and allied fields since the war. This effort is now producing not only practical information as regards protection of military personnel from thermal stress, but is resulting in advances of a basic scientific nature. It is in this latter category that the most interesting and perhaps, in the long run, the most important contributions are to be found. The development of new instrumental methods for the study and analysis of environmental stress and for the measurement of thermal strain in man and animals is a good index of the vigorous interest in the heat and cold stress-strain relationships. In reviewing the work of the past two years (July, 1947 to June, 1949), it is evident that the major interest has been in Man's responses to internal and external stress, and the animal work which has been done has been directed towards shedding further light on human physiology. For that reason, the focus of this article will be on the human responses to thermal stresses. The literature will be discussed in the following categories: New Methods; Responses to Cold; Responses to Heat; Measurements of Blood and Tissue Temperature; Vascular Responses to Thermal Stimuli; Studies in Thermal Sensation; and Temperature Regulation.

### NEW METHODS

Although the idea of measuring heat loss by means of a "gradient calorimeter" is not new, Benzinger's development (1) of a rapidly responding calorimeter based on this principle bids fair to open a new field of study. Using a thin layer of insulating material to reduce the thermal inertia of his calorimeter, Benzinger can obtain a 100 per cent response to changes in total heat loss in a few seconds. The sensitivity of the calorimeter is maintained by using

several hundred thermocouples in series across the gradient layer. To accompany this rapid measurement of heat loss, Benzinger has added the interferometer for measuring oxygen consumption and carbon dioxide production (2). Although the gradient calorimeter is easily built and is inexpensive enough for even modestly equipped laboratories, the rapid and accurate measurement of oxygen and carbon dioxide is difficult and expensive. Even with the use of the infrared gas analyzer (3), drifting and calibration difficulties are considerable and the cost is great. The newly introduced Pauling oxygen meter is an excellent instrument for rapid recording for those laboratories that can afford it (*ca.* \$1500), and the mass spectrometer has also been successfully adapted to measurements of metabolic carbon dioxide and oxygen (4). However, with the new methods of calorimetry which have speeds comparable with the thermal responses of man, the future seems bright for new studies of fever and the transient effects of thermal stress. A simpler but somewhat slower method of gradient calorimetry has been adapted for animal measurements, and experimental periods of 15 min. are possible (5).

Rapid recording of water loss (6, 7) due to evaporation from the skin and lungs has been accomplished with an infrared gas analyzer. These studies have revealed fluctuations in the sweating rate within four to six seconds, as well as longer periods of several minutes. The shorter periods are undoubtedly related to the fluctuating character of vasomotor activity, and the longer periods to the release and drying of sweat which is a part of the pattern of regulation of skin temperature in warm environments. Krogh (8) has introduced a method of continuous recording of air temperature and humidity under the clothing with a micro "climate" recorder. Air temperature is recorded by a bimetallic spring and humidity by a human hair; both records are read by a microscope from a sooted glass dial of wrist watch dimensions.

A novel method of controlling the temperature of a test room by means of a clothed metal artificial man has been described (9). The dummy is heated at the rate of 73 kcal. per hr., and the "skin temperature" of the dummy is maintained at 33.4°C. by regulating the temperature of the environment.

A new instrument for measuring the total radiation load in the out-of-doors environment has been introduced (10, 11). Instead of arriving at an index of unknown proportionality to the radia-

tion, the pan-radiometer measures the radiation in physical terms of calories per square meter per hour, and in addition permits the determination of the sun's radiation as separate from the long-wave infrared radiation to the sky and terrestrial objects. The need for such an instrument has long been recognized, particularly in the study of the out-of-door heat load.

The measurement of skin temperature continues to intrigue the interest of experimenters. Thermistors and thermocouples with ingenious mountings have been proposed (12, 13, 14). However a critical comparison of the various devices for skin temperature measurement indicates that radiometry is the most dependable if the most difficult method. Bare wire thermocouples attached to the skin with collodion or adhesive tape can, under carefully controlled conditions, give skin temperature readings to  $\pm 0.5^{\circ}\text{C}$ . (15).

A new and important technique is that of introducing thermocouples into the vascular system through small catheters (16). This has permitted direct measurement of intravascular temperatures in the brain, deep viscera and extremities. Much of practical and theoretical interest attaches to these studies. The heating of tissues by means of microwaves appears to offer the possibility of producing deep local rises in tissue temperature (17). As a tool for studying temperature regulation, this procedure may prove particularly useful.

#### RESPONSE TO COLD

*Hypothermia.*—The discovery of the fact that warm blooded animals can exist for several hours with reduced internal temperature has provided an excellent opportunity to study temperature effects over a wider range than formerly. The results of some of the studies in this useful field are briefly summarized as follows:

A close relationship between body temperature, arterial pressure, and blood sugar level of the chicken has been found. As arterial pressure changes occur within a few seconds after application of the thermal stimulus, a neural mechanism is implied. The blood sugar response is delayed for some 30 min., and this delay is attributed to a hormonal influence (18, 19). The feeding of whole liver is reported to increase the ability of rats to survive in the cold over rats fed a diet complete in the known components of the vitamin B complex. This evidence points to the existence in

liver of a new vitamin (20). The  $Q_{10}$  for experimental convulsive seizures in rats has been determined in relation to seizure threshold to be 1.6, that for seizure duration 2.8, and that for recovery, 2.0. The possibility of three different chemical reactions underlying these functions is suggested (21). Rats with internal temperature near 25°C. were observed to be hypersensitive to intravenous injection of potassium chloride, although the administration of large amounts of glucose gave partial protection (22). Some effects of hypothermia on nerve conduction in the hibernating golden hamster and the rat have been measured and compared. Nerves of hamsters continued active to temperatures as low as 3.4°C. whereas rat nerves would not conduct at temperatures lower than 9°C. These differences are regarded as evidence of intrinsic adaptation to cold in hibernators not found in nonhibernators (23). Rapid cooling of fertilized rabbit ova *in vitro* was found to be more harmful than slow cooling. Ova could be maintained at 10°C. for 144 to 168 hr., but at higher or lower temperatures deleterious effects were observed (24). A potentially important observation is that hypothermia in frogs inhibits the manifestation of toxic effects of ionizing radiations. Protection from the effects of the irradiation was not afforded by the low temperature, however (25).

The mechanisms of the lethal effects of cold on warm-blooded animals has aroused considerable interest. White rats less than 10 days of age were cooled to 3°C. for as long as 108 min. and upon rewarming recovered in the majority of cases (26). The heart stopped beating at 9 to 3.5°C. and all other signs of life were absent during the hypothermia. In 10 per cent of the animals not surviving the low temperature, damage to the heart by anoxia was suspected. Rats up to 27 days of age could survive a two-hour hypothermia at 10°C. in a nitrogen atmosphere and for shorter times at lower or higher temperatures. The presence of air enhanced survival above 5°C. and oxygen greatly prolonged it up to 12°C. With increasing age the tolerance to anoxia was lost before that to cold. During the cooling of young rats there was a slight transient rise in metabolism and rats younger than 10 days had no observable oxygen consumption for 108 min. when a body temperature of 3°C. was reached. Electrocardiograms showed that heart rate and conduction rate of the cardiac impulse decreased with body temperature. At 10°C. the heart stopped. On rewarming 10 per cent of the ani-

mals died showing heart block and irregular QRS impulses, suggesting injury to the atrioventricular node and conduction system. Experiments with excised turtle hearts also indicate damage to the sinus tissue by cold (27). On the other hand adult rats could not survive colonic temperatures lower than 14°C. regardless of methods employed to prolong survival (28, 29). Guinea pigs were observed to succumb immediately when body temperatures as low as 22° to 18°C. had been reached (30). Dogs were able to survive hypothermia to about the same extent as the adult rats. A rectal temperature as low as 11.7°C. for a very brief period was survived in one instance. The average lethal temperature for dogs was observed to be 14.9°C. During the cooling process the pulse rate and blood pressure fell linearly with the body temperature, and below 20°C. brachycardia became pronounced. Atropine and vagotomy had no effect on heart rate at these temperatures (31, 32). Cardiac output and oxygen consumption also fell with body temperatures between 35° and 25°C. (33). Consciousness persisted and reflex activity persisted to a limited degree for cerebral temperatures higher than 24.5° to 28°C. A potentiation of the cold narcosis by pentothal anesthesia was observed (34, 35).

At the present time the cause of hypothermic death is not known, although irreversible damage to vital organs such as the heart has been demonstrated to follow hypothermia. A further search in the direction of differences in the effects of cold on hibernating and nonhibernating species may shed additional light on this matter.

*Cold environments.*—Body temperature can be maintained in the normal range for 1 hr. by pigeons at -85°C., chickens at -50°C., rabbits at -45°C., and white rats at -25°C. (36). The metabolic rate of pigeons after 4 hr. at -40°C. is about 3.5 times the basal rate and varies between three and five times basal until the terminal drop in body temperature after about 80 hr. Liver glycogen is almost depleted in 24 hr. (37). A retention of ascorbic acid in the tissues of white rats when exposed to a cold environment, and a consequent preventive effect on adrenal hypertrophy, has been demonstrated. This retention is part of an acclimatization process (38). Cold has been demonstrated to have a direct stimulating effect on certain smooth muscles, the retractor penis muscle of the dog, the nictitating membrane of the cat, and of the arterio-

venous anastomoses of the skin (39). This effect may be of importance in temperature regulation and in the production of "cold pain."

Search for evidence of acclimatization of men to low environmental temperatures has continued with little success as yet. The resting metabolism of men and the metabolic energy required to do a standard amount of work were found to be greater in the cold ( $-29^{\circ}\text{C}.$ ) than in the warmth ( $24^{\circ}\text{C}.$ ). Upon continued exposure to cold, a small but definite decrease in the caloric requirement for work was observed, although this could not be attributed to acclimatization definitely (40). The moving of bulky clothing may have had the effect of increasing the energy required for a standard amount of work. An after-stimulating effect of cold occurred in the form of an increased resting metabolism when the men were returned to a warm environment following eight days of exposure to cold. This observation is at least suggestive of some adaptive change due to cold exposure. The caloric value of food intake of soldiers stationed in the Arctic, 5000 kcal. per day, has been compared with that of men in the tropics, 3100 kcal. per day. This difference has been attributed to increased voluntary activity, although in part it may be due to increased "resting metabolism." A linear increase in food intake has been noted with increasing cold for men stationed in climates varying from  $93^{\circ}\text{F}.$  to  $20^{\circ}\text{F}.$  mean temperature (41). For relatively short exposure (nine days) to intense cold ( $-32^{\circ}\text{C}.$ ) food appears to be secondary in importance to the adequacy of clothing (42). That the increase in food requirements in the cold may come largely from carbohydrates has been shown (43, 44). Rapid air movement in addition to cold brings on more quickly the demands for higher heat production, and the amount of extra heat produced is proportional to the wind velocity (45). The stimulating effect of the wind could not be correlated with the rate or amount of body heat loss.

Evidence has been advanced that the diuretic effect of cold exposure in man is due to stimulation of the posterior lobe of the pituitary (46), inhibition of cold diuresis being brought about by intramuscular doses of pitressin. Cold baths have the effect of assisting recovery from fatigue (47) and of combating the orthostatic hypotension seen in tilt table experiments (48).

Efforts continue in the search for better methods of insulating the body against cold environments and of rewarming individuals following exposure to cold. Protection of the extremities at  $-30^{\circ}\text{F}.$

has been accomplished most effectively by making sure that the body was in positive thermal balance (49). This very practical observation shows that the temperature of the hands and feet is for the most part dependent upon their blood supply and only to a small extent upon the ambient temperature and glove insulation. A practical method of maintaining a suitable "private climate" has been found in the internal ventilation of clothing by air of the desired temperature (50). The development of textiles having high insulating properties and yet light and flexible enough for ordinary civilian usage has been pointed out (51) as an important factor influencing the heating of homes and buildings.

Experiments on rewarming of humans after exposure to cold have not added much to the information gathered during the war. Although hot baths to produce rapid warming are probably the most effective means of rewarming, strenuous exercise when the victim is capable of it can also restore body heat. Sleeping bags, moderated exercise, warming face and hands with thermal radiation were not effective (52).

#### RESPONSE TO HEAT

The range of temperature above the neutral zone has not elicited the interest from investigators concerned with human tolerance and response which the lower range has aroused. However, from the standpoint of temperature regulation, vascular responses, and human ecology, this is probably the more interesting temperature zone. An outstanding study of the tolerance of men to heat has been made on four college students exposed to ambient temperatures between 100°F. and 250°F. with low humidity for short periods (53). Physiological reactions were summarized as follows: (a) Skin temperature rose continuously, the rate of rise being greater at the higher temperatures. A maximum mean skin temperature of 107°F. was observed at 240°F. with clothing of medium light wool and cotton union suits. (b) Heart rate rose with skin temperature, reaching rates as high as 172 per min. (c) Systolic arterial pressure rose during exposure, but diastolic pressure was variable. (d) No definite heart changes could be seen from electrocardiographic changes. (e) Rectal temperatures tended to rise after a delay but were variable. (f) The temperature of the exhaled air, measured at the mouth, changed with ambient temperature. (g) Respiratory rate increased with ambient temperature to two or three times resting level. (h) Oxygen consumption

roughly paralleled ventilation rate. (i) Rate of sweat loss was highly variable. (j) Subjective symptoms were dyspnea, deep irregular respiration, irritability, and dizziness upon removal from the oven. From these studies a physiological measure of thermal strain was suggested as composed of heart rate and skin temperature. The tolerance times for two male subjects were:

Ambient Temperature	Mean Tolerance Time
180°F.	49 min.
200°F.	33 "
220°F.	26 "
240°F.	23.5 "

In these short exposures, the superficial tissues were undoubtedly serving as a thermal sink and, as such, acting as a protective layer about vital tissues. The increased heart and respiration rates may possibly have been due to painful stimulation of the skin.

Survival of cats with rectal temperatures of 110°F. has been noted (54), although dogs do not survive for more than a few minutes when the rectal temperature has reached 109°F. If allowed plenty of water dogs can live indefinitely at environmental temperatures of 130°F., although rabbits and guinea pigs do not withstand temperatures higher than 110°F., rats and mice 102°F. Experiments on men indicated that sweating rates as high as 3.5 kg. per hr. could be sustained for several hours in a saturated atmosphere at 94°F. Dehydration was found to be an important factor affecting heat tolerance. The rise in body temperature during heat exposures was proportional to the water deficit, although sweat secretion was active at all levels of dehydration. During dehydration fever, the flow of blood to the periphery was not always maintained due to decreased blood volume.

Although positive evidence of heat adaptation has long been available, new information has been obtained under controlled conditions in an effort to study the nature of this phenomenon. Three healthy men were exposed to heat (107°F. dry bulb, 98°F. wet bulb) for five and a quarter hours in 19 successive periods to acquire heat acclimatization (55). The state of acclimatization was determined by the decrease in the amount of rise in rectal temperature caused by a standard work procedure. This was followed by fourteen exposures to cold (-20°F.), by five re-exposures to heat, a five week interval of no exposures, and three final re-

exposures to heat. The cold exposures were found to have no influence on the acclimatization to heat and the heat acclimatization can be maintained indefinitely in normal environments by occasional re-exposures to heat. It would be interesting to observe the effects of injections of adrenal cortical hormones upon this adaptation. In fact, a complete study of the heat-adapted man as regards his thermal responses would be profitable. For example, the correlation coefficients of basal heat production of heat-acclimatized males with body weight have been found to be 0.83 for lean men and 0.78 for well-proportioned men, rather than 0.67 for unacclimatized males (56, 57).

Women, even in exposures of a few hours to moderate heat, show adaptive effects by a fall in metabolism of as much as 8 to 18 per cent (58). A similar adaptive effect has been demonstrated in American women living in Arizona (59). Galvão proposes the theory that basal metabolism in Northern climates is composed of two fractions, i.e., the first related to the mass of active metabolic tissue and the second a stimulation due to cold. In the tropics, he feels the first of these fractions is predominant so that the basal metabolism in the warmth-adapted men does not follow the surface area law. In temperate zones, the sum of the two effects is seen with the second fraction causing a stronger dependence on the surface area. However, as the recent measurements of basal metabolism in the temperate zone are generally lower than the older standards based on the surface area law, opinion must be reserved in regard to interpretation of differences as small as those reported by Galvão.

An extensive report of the effects of tropical fatigue on nearly 2,000 soldiers stationed in the South Pacific area has been made by Lee & Macpherson (60). The principal facts emerging from the study were: (a) there was only slight increase in vasomotor instability; pulse rates and arterial pressure were unaffected; (b) slight weight loss; (c) 57 per cent contracted mild or moderate skin disease; and (d) reduced efficiency as estimated by subjects and officers.

Analysis of the chloride and creatinine loss during work in hot, humid environments has been studied by Ladell (61, 62). With increased rates of sweating, the creatinine content of sweat decreased. The chloride content of whole body sweat was found to be the same as that from a single arm, over a large range of sweating rates.

Heat death in rats has been shown not to be due to a toxic agent produced in muscle tissue (63), and in chicks is more likely to be attributable to thermal damage to the central nervous system (64). A sensitization to ionizing radiation (x-rays) following exposures to heat has been demonstrated (65), and the author discusses the possible practical usefulness of thermal sensitization in the treatment of malignant growths.

#### TEMPERATURE OF BLOOD AND TISSUES

The measurement of intravascular temperatures has been a particularly active field of study in the last two years. The large variation in the intra-arterial temperature (21°C. in the radial artery and 37.5°C. in the brachial artery) has been emphasized by Bazett and his associates (16, 66, 67). These workers have also pointed out the importance of the thermal interchange between the warm blood of the arteries and the cool blood returning from an extremity. The application of external heat and cold caused profound changes in the intravascular temperatures in the large vessels of the extremities. By introducing a thermocouple into the internal jugular vein and comparing this temperature with the rectal temperature, it was found that the two are not identical and do not change in an identical way (68). The deviations though small may be significant. A similar study was made on 21 afebrile patients and indicates that the femoral artery may give a better average of mixed deep temperature than the rectal temperature, by a few tenths of a degree Centigrade (69). Attention also is called to the fact that the brain, liver, and large bowel are tissues producing heat and have temperatures higher than that of the average circulating blood (70). The variability of deep vascular temperature has raised questions regarding homeothermy as a concept. It seems to the reviewer that no essentially new questions have appeared in this regard, but rather a clarification of the nature of the thermal interchange that makes possible a relatively uniform internal temperature. Practical considerations make the rectal temperature the most useful index of internal temperature, and as the rectal temperature varies somewhat with the depth of insertion of the thermometer, perhaps it will be possible to choose a depth which will have a temperature which corresponds with the average, mixed, deep temperature.

*Tissue temperatures.*—A few studies of tissue temperatures have

been made profitably. Pennes (71) has measured rectal, brachial artery, and deep forearm temperatures and has determined that the blood flow acts as a warming agent to all tissues of the relaxed forearm. Measurements of tissue-blood thermal gradients were also made to evaluate the effects of local heat production and circulation. From these data, Pennes concludes that calculations of "peripheral conductance" from total heat loss and skin and rectal temperature do not give a true picture of the level of blood flow in any locality. This conclusion is undoubtedly correct, and the average peripheral conductance is of value only in estimations of average levels of superficial blood flow. The concept of a uniform "core" temperature and a variable skin and peripheral tissue temperature gradient is idealized and represents only average function. As important thermal interchanges occur between the deep veins and arteries, as well as in deep visceral and superficial tissues, the "total peripheral conductance" concept should never be applied specifically to a local process, but should be used as a measure of the functional control exercised by the entire vasomotor apparatus on the rate of heat lost from the body. The fact that each body area behaves in a different manner from the average is important but does not invalidate observations and conclusions drawn from the average measurement.

The importance of the level of average skin temperature as an index of comfort has been pointed out by Yaglou & Consolazio (72). Comfort is associated with a mean skin temperature of about 92.5°F., sensations of cold with a skin temperature lower than 92°F. and heat with skin temperatures of 95°F. and higher. These measurements were made on men and possibly a different set of skin temperature values would be found for women.

Temperatures in various parts of the pericardial sac of the dog have been studied in relation to the T-wave (73). It was found that the T-wave changed 1 mm. in amplitude for each one-degree change in temperature of the left ventricle. It was concluded that the normally occurring variations in heart temperature can account for at least part of the amplitude and direction change of the T-wave.

#### VASCULAR RESPONSES TO HEAT AND COLD

Interest in this subject has taken three rather well defined directions, namely, reflex responses to warming or cooling parts

of the body, direct responses of peripheral vascular system to heat and cold, and the relationship between skin temperature and blood flow. A generalized vascular response in the form of changes in systemic blood pressure with local heating and cooling of the brain has been demonstrated by Rodbard, Taylor & Ferguson (74) in turtles. These authors call attention to the close phylogenetic and anatomical relationship of the controls of body temperature and arterial pressure.

Heating of the face with infrared radiation has been shown to be a more powerful stimulus in producing reflex dilatation in men exposed to cold than the same intensity of stimulus applied elsewhere on the body (75). This effect is very likely due at least in part to the greater sensitivity of the face as regards perception of thermal stimulation (75a). Some effect may also have been produced by heating the tissues and blood near the brain. The importance of the face as an exposed thermosensitive area in the thermoregulatory adjustments of the clothed man is apparent from this study.

The thermal lag in the tissues of the extremities affects the estimations of blood flow made from measurements of skin temperature (76, 77, 78). Also, when environmental temperature is changed rapidly, the skin temperature of a hand may be rising (or falling) with little or no change in blood flow to the extremity. This lack of parallelism between skin temperature and peripheral blood flow has been noted before, as the average skin temperature falls during exercise due to sweating, although the superficial blood flow may be much increased. However, with proper corrections for the effects of the direct environmental cooling and heating, skin temperature can be used as a dependable index of blood flow. As Pennes has pointed out, the heat supply to an extremity is almost entirely dependent on the blood stream. The promptness of the vasoconstriction in the hands and feet upon exposure to cold (97 per cent of maximum vasoconstriction of the fingers in 3 min.) has been shown to be much more rapid than the corresponding fall in skin temperature (77). This difference is, of course, due to thermal lag; and upon warming an individual previously exposed to cold, the skin temperature rises much more rapidly than does the blood flow.

Study of the reflex effects in one extremity of heating and cooling of the other extremity shows a delicate vasomotor balance existing in lightly clothed individuals at temperatures of 21 to

25°C. These effects are not apparent in warm (above 30°C.) and cold (below 20°C.) environments (79). Although the reflex effects cannot be seen in warm environments, a careful balance between heat loss requirements and general vasomotor response can be demonstrated calorimetrically. It is possible that the stimulating effects of the environment on the thermal receptors in the skin control the vasomotor responses in both the hot and cold environments. Thus, many of the effects of reflex heating and cooling on vasomotor activity (80, 81) may be explained by the relative intensities of the thermal stimulation of the skin by the environment and by the local experimental stimulus.

The direct effect of heat and cold upon blood vessels of the extremities has been demonstrated in the denervated and detached limbs of dogs (82). Cold causes a sudden 90 per cent complete vasoconstriction when the animals have been exposed long enough for the denervated paw to reach  $22^{\circ}\text{C.} \pm 2^{\circ}\text{C.}$  by environmental cooling alone. A sudden rise in paw temperature was noted following exposure of the paw to warm air. That this is a purely local effect of the cold and warmth on the paw was demonstrated by persistence of the reaction when (a) the adrenal glands were extirpated, (b) when the leg was disconnected from the body except for the procainized artery and vein, and (c) when the paw was chilled while the animal's body was heated. This type of vasomotor response may be related to the production of cold pain as the effect occurs only when the limb has been chilled to  $22^{\circ}\text{C} \pm 2^{\circ}\text{C.}$  The threshold for cold pain in the hand has been shown to be  $18^{\circ}\text{C.} \pm 2^{\circ}\text{C.}$

The changes in muscle temperature following denervation have been reported by Kemp, Tuttle & Hines (83). There is an immediate rise in muscle temperature and blood flow following denervation; but after prolonged periods, the temperature and blood flow fall to a subnormal level paralleling muscle atrophy. Heating the denervated limb by diathermy caused a greater rise in the denervated muscle temperature than in the contralateral control due to the fact that the subnormal blood flow could not carry away the heat developed by the electromagnetic induction.

#### STUDIES IN THERMAL SENSATION

This important physiological response to thermal stimulation has been largely neglected in the war years. However, as the appreciation of the role of these sensations in the regulation of

body temperature has increased, the interest in this direction has correspondingly increased and new data have become available.

Using thermal radiation as the stimulus, Ebaugh & Thauer (84) have shown that the threshold to warmth is constant for subjects exposed nude for several hours to environmental temperatures ranging from 15° to 38°C. The cold threshold was the same as the warmth threshold in environments from 15° to 25°C., but between 25° and 33°C. the cold threshold increased almost three-fold, remaining at the higher level for higher temperatures. The authors offered increased peripheral vasodilatation as a possible factor bringing about the alteration in cold threshold, but suggested no explanation for the constancy of the heat threshold. These observations are of practical value in understanding the role of the periphery in temperature regulation in man, as they are evidence indicating that the skin can recognize levels of temperature as well as changes in thermal gradients in the skin.

From the new climatic laboratory in Copenhagen have come some studies on the practical side of thermal sensation, namely, comfort. Nielsen (85) has shown that heating the floors has an insignificant effect on foot temperature and comfort as compared to the over-all thermal balance of the body as a whole. Bøje, Nielsen & Olesen (86) have carried out experiments in which subjects were irradiated from warm radiators on one side of the body and cold radiators on the other; an over-all comfortable temperature was maintained. Skin temperatures were measured on both sides and estimates of thermal sensation were made for each side. The subjects, although comfortable, reported feelings of cold from the cold side and warmth from the warm side; skin temperature in hands and feet was 1° to 2°C. lower on the cold side. In several subjects there occurred spontaneous pain from the cold side with some myalgia. The authors call attention to the fact that feelings of comfort alone are not sufficient protection against harmful thermal conditions in the environment, a point well recognized by athletes and others following periods of strenuous exercise.

Nielsen (87) made a study of thermal sensations in and near the comfort zone in young men, young women, and old men. From these studies he concluded that the sensation of "uncomfortably cold" is due mainly to the cooling of the extremities, particularly the feet. He could find no consistent relationship between (average) skin temperature changes and the sensations of heat and cold, but some relationship appears when the "steepness of the tempera-

ture gradient through the skin" is considered. In view of the changes in thermal sensation thresholds in the comfort zone and the lack of other similar data, difficulties must be expected in interpreting this type of experiment.

The response of spinal man to hot and cold immersion of the lower extremities has been studied by Macht (88). On the hot side withdrawal was elicited by water warmer than 50°C. The withdrawal is interpreted as due to stimulation of free nerve endings subserving pain. On the cold side the withdrawal is interpreted as due to stimulation of Krause endings, although stimulation of "cold pain" was not ruled out.

#### TEMPERATURE REGULATION

An exceptional amount of interest has been shown in this subject since the war as a result of the stimulation received from researches started in military laboratories. Present thought is directed towards the following objectives: (a) obtaining better understanding of the neurological elements concerned with temperature regulation; (b) investigation of the functional characteristics of the central thermoregulatory center; (c) clarification of understanding as regards responses of man and animals to internal and external thermal stresses. It will be convenient to discuss these topics in order.

*Neurological studies.*—Keller (89) in a particularly clear-cut way has shown that section of the entire pons in dogs except for the pyramidal tracts affects to a surprisingly small extent the ability of the animal to maintain body temperature in cold environments. The dogs showed increased metabolism in the cold, and it must be concluded that nerve fibres having to do with heat maintenance in the cold must descend in the cerebrospinal bundles. An interesting question here is whether section of the pyramidal tracts alone will seriously impair heat maintenance powers. The above evidence would indicate that sensory responses to cold from the trunk and extremities are not important for thermostasis in dogs. It is quite possible that the head of the dog contains the temperature receptors.

Chambers & Windle (90) have found that injection of pyrogenic extract into cats with chronic hypothalamic lesions interrupting the thermoregulatory pathways caused febrile responses although shivering and piloerection were absent. These preparations were also unable to adjust to sudden changes in environmental

temperature. Spinal preparations (cervical transection) gave no responses to the pyrogens and could not adjust to sudden temperature changes. They have also shown by ablation experiments that a principal site of action of the pyrogen is in the medulla. Thus, the central heat regulator must be thought of as extending from the anterior hypothalamus to the medulla.

Vasomotor changes in the form of elevated skin temperature have been found in monkeys following bilateral ablation of area 13 (91). These changes are persistent in chronic preparations and probably affect temperature regulation, although no mechanism for these vasomotor changes is as yet known.

Buchanan & Hill (92), using measurements of the optical density of hypothalamic tissue slices as an index, have shown that the increase in myelin in the hypothalamus in rats parallels the development of ability to regulate body temperature. These authors do not claim that this myelination is the principal factor involved but feel that it may contribute to the acquisition of the capacity for temperature regulation.

A temperature sensitive center in the brain of poikilotherms which manifests itself principally in the control of arterial pressure with changes in temperature has been reported by Rodbard (93, 94). In the normal turtle, the arterial pressure was observed to increase from 20/13 mm. Hg at 10°C. to 40/33 mm. Hg at 35°C., whereas in the pithed animal, the arterial pressure was constant within the 25°C. range of temperature. It would seem possible that much can be learned from the study of more primitive forms that will assist in understanding temperature regulation in man.

*Metabolism of the heat regulating center.*—Based on the assumption that temperature regulation must depend in some predictable way upon the metabolic level of the regulating centers Hall, Field & Grant and their associates (95 to 98) have carried out a series of careful studies of the metabolic rate of brain tissue under conditions which are known to influence the temperature level in the intact animal. The results of this important study are:

(a) The change in metabolic rate with temperature of hypothalamic tissue is the same as that of cortical tissue. This means only that the cells of the thermoregulatory center apparently do not have an unusual  $Q_{10}$  for oxygen consumption.

(b) Chemical agents which alter the thermostatic "set" of the regulating center (pyrogens and antipyretics) do not alter the

aerobic or anaerobic metabolism of brain tissues. Tissues of the hypothalamus itself have not been studied as regards the effects of pyrogens because of the small amount of tissue available in the animals studied. Before this question can be finally settled, however, the cells of the hypothalamus alone will have to be investigated.

(c) There was no difference in the cholinesterase activity of normal and febrile rabbit brain tissues, indicating that thermostatic set is not reflected by quantitative changes in the cholinesterase assay.

Although these results are negative from the point of view of ascertaining the functional characteristics of the heat regulating center, they clarify understanding as to more profitable lines of search. Perhaps the rate of discharge of nervous impulses recorded from the hypothalamus would correlate with brain temperature and with pyrogenic activity.

In the course of their studies these workers have concluded:

(a) That typhoid paratyphoid vaccine (TPT) has two distinct actions in the animal: pyrogenic in doses between 0.0002 cc. per kg. and 0.02 cc. per kg., and toxic reactions with greater amounts which cause erratic fevers, fall in arterial pressure, etc.

(b) Fever from TPT in rabbits is due to a restriction of heat loss, that is, upon altered "physical regulation."

(c) TPT raises the threshold (as measured by the rectal temperature) for the appearance of thermal polypnea whereas magnesium chloride has the opposite effect. Heagy & Burton (99) have obtained similar results although looking at the effects of magnesium chloride in another way, that is, its effect on dogs regulating against external heat and cold. If the dog is regulating against heat or is in a neutral environment the injection of 1 M magnesium chloride will cause a drop in body temperature. In cold environments the injection has less effect unless the dose is large enough to cause a paralytic action.

(d) Urethane causes a fall in rectal temperature, not by lowering the threshold to thermal polypnea and vasodilatation, but affecting more peripheral mechanisms than the primary thermoregulatory centers.

*Temperature regulation against "internal stress."*—"Internal stress" is meant to refer to the thermal changes that originate within the body, such as work and exercise, and the effects of chemical agents such as pyrogens, antipyretics and anesthetics.

"External stress" thus refers to changes in the temperature and humidity of the environment from those of "thermal neutrality" or the "zone of vasomotor control," etc. Revealing experiments often combine the two forms of stress and these will be discussed under internal stress.

Asmussen & Nielsen (100) have studied the rise in rectal temperature following a standard amount of work performed in one instance with the legs and in another with the arms. It was observed that the temperature rise was less when the arms were used than when the legs were employed. The authors, as a result of a comparison between the temperature rise of the stomach and that of the rectum, concluded that a different "setting" of the heat dissipating center occurred during work with the arms than that during leg work. The internal temperature measured in any one place is the result of local processes and of those occurring at a distance but closely linked by blood flow. Thus, it is probable that the large veins from the working leg muscles carry more heat into the rectal regions than do the veins from the arm muscles. More direct evidence of a difference in temperature of hypothalamic blood would be required to establish a difference in "reset" of the heat regulatory system in this experiment.

Robinson (101), observing the control of sweating rate in working men, remarked that, although the rectal temperature rose as the work increased, the skin temperature remained constant. He concluded that the effect of the work was a direct one on the heat regulatory center and that the rate of sweating was controlled there. Robinson also observed that for the same working rate, the rectal temperature rose to the same level for any environmental temperature between 10°C. and 32.5°C., although the sweating rate varied, increasing with increased environmental temperature and vice versa. The first of these clear-cut observations support other evidence that at constant environmental temperature, the central thermoregulator offers the first protection against thermal stresses of internal origin (changes in metabolism). Much other evidence has shown that with a constant (or basal) metabolism, first protection against environmental temperature changes is afforded by the thermal receptors in the skin. Robinson's second series of experiments falls into this category and extends previous observations to include higher levels of metabolism. Thus, it appears likely that the increase in metabolic rate causes a specific amount of rise in internal temperature which, through

stimulation of the central thermoregulatory center, calls for a definite increase in heat loss from the skin. Also, for any thermal environment, the reaction of the environment on the receptors in the skin controls the amount of vasomotor activity and the sweating rate which effect the necessary heat loss.

Park & Palmes (102) have shown that the strain of work in hot environments can be relieved only when sufficient sweat can be secreted over the body surface. This acclimatization to work in hot environments results, as shown by Kuno, from the increase in number of potentially active sweat glands over the skin surface so that sweating can be done more efficiently and with less dripping. Park & Palmes (103) in a brilliant series of experiments have shown that the strain on the central thermoregulatory center produced by circulating pyrogens is dependent solely on the pyrogen and independent of the environmentally induced thermal strain. These authors injected pyrogens into healthy humans exposed nude to environmental temperatures from 25°C. to 43°C. and observed that the rise in body temperature was the same in all environments. The pattern of development of the fever was different, however. In the cool environments, vasoconstriction and an increase in metabolism of 300 per cent brought about the prompt rise in body temperature. With increased environmental temperature, abrupt cessation of sweating and vasoconstriction had the greatest effect in raising the body temperature; the metabolic increase was small and short in duration—five to ten minutes. The amount of the adjustment in metabolism, sweating, and vasoconstriction was always just that necessary to raise the internal temperature two to three degrees Centigrade. The experiments are quite analogous to those of Robinson, mentioned above, and to those of Nielsen, and demonstrate clearly the functional autonomy of the central heat regulatory center in dealing with internal thermal stress.

Wells & Rall (104) have confirmed the above observations by experiments on curarized dogs. They found that pyrogens injected into dogs previously treated with curare, abolishing skeletal muscle activity (shivering), caused a prompt rise in body temperature as a result of vasoconstriction (75% of the effect) and to a lesser extent (25%) of increased metabolism. The authors attribute the increased metabolism to a  $Q_{10}$  effect, which seems reasonable. The "chemical regulation" of Rubner is thus shown not to be a necessity in the production of fever in warm and hot environments. In

cool and cold environments, increased metabolism is essential to hyperpyrexia.

A series of experiments reported by Hemingway (105) takes up the subject from the point of view of depressing the thermoregulating center by ether, rather than stimulation by pyrogens and exercise. The experiments were in a preliminary stage from which it could be concluded only that 90 to 150 mins. after cessation of the ether anesthesia the ability of the dogs to maintain normal body temperature had recovered, and that ether had least effect on shivering. A series of experiments at different temperatures and in connection with pyrogens, curare, etc., should yield other interesting information as to the functions of the biological thermostat. Kottke *et al.* (106) have made experiments on men and dogs in which the hypothalamic centers of thermoregulation have been depressed by hypoxia. This depression caused the experimental subjects to respond minimally to cold exposure. It would be most interesting to observe the response of the hypoxic man to elevated environmental temperatures, as it is conceivable that hypoxia and elevated blood temperature have like effects on the hypothalamic centers.

*Temperature regulation against "external thermal stress."*—The regulatory processes which occur automatically with changes in the environmental temperature and humidity are the physiological strains elicited by the thermal stress of the environment. This stress has its first effects on the skin and the temperature sensitive endings found therein. Hardy & Goodell (107), observing the rise in rectal temperature ( $0.3^{\circ}\text{C.}$  to  $0.8^{\circ}\text{C.}$ ) in individuals exposed to cold ( $16^{\circ}\text{C.}$ ) after previous equilibration to a warm environment ( $31^{\circ}\text{C.}$ ), concluded that the stimulating effect of the cold on the skin was the principal agent regulating against cold. Also, individuals exposed to a warm environment, after previously being chilled, undergo a fall in rectal temperature to subnormal levels, but show at the same time strong vasodilatation and even slight sweating, again indicating that regulation was arising from the skin and not the central thermostat. Indeed, available evidence from all sources indicates that the particular level of thermoregulatory adjustment is a balance established between the effects of the stimulation of heat and cold receptors, and the excitation of the hypothalamic centers by the level of blood temperature. Depending on the intensity of the stimulus to one or another of

these, the thermal adjustment changes. The intensity of the sensations of heat and cold is known to depend upon the size, location, and vasomotor tone of the skin area stimulated and upon the rate of change of the thermal gradients in the skin; the hypothalamic centers are affected by temperature change (exercise, for example), chemical stimulation (pyrogens, anesthetics, etc.), hypoxia, and electrical and mechanical stimulation. With so many variables to deal with, it is not easy to vary only one factor for experimental purposes, while keeping all the others constant.

Burch (108) has determined that the threshold for sweating of subjects of varying ages is an environmental temperature of  $34.4^{\circ}\text{C}$ . with a relative humidity of 50 per cent. This combination of temperature and humidity is, of course, only one point in a family of curves involving air temperature and velocity, humidity, radiation, metabolic rate, etc. Extension of these observations would yield other valuable data.

Randall, Deering & Dougherty (109) have studied the reflex sweating produced by the local application of radiant heat to an arm. Sweating was observed on the irradiated and control arm in spite of occlusion of the blood flow from the heated arm. Upon release of the occlusion, the sweating in both arms was markedly inhibited. A hormonal or perhaps a sensory effect may account for the inhibition.

Mole (110) has proposed a refinement of the "wetted" skin area, suggested by Gagge (118), in the form of the "relative humidity" of the skin. This proposal is quite similar to the original concept of Büttner (119), who in 1934 discussed the vapor pressure gradient from the skin to the ambient air. The interpretations of Mole and Gagge are readily fitted into Büttner's more general discussion.

Detailed studies (111, 112) of the sweating rate show that sweating occurs in short cycles, eight seconds and less, and in much longer cycles of several minutes. There is an apparent synchronism in the bursts of sweat gland activity in different parts of the body, excepting the palmar surfaces of the hands and plantar surfaces of the feet, which respond to excitement, deep breathing, etc., more than to thermal stimulation.

In a study of the heat loss from the feet, Love (113) has found that the feet do not follow a simple Newton's Cooling Law in cold and hot environments. The roughening of the skin in the cold is

given as a possible explanation, to which might be added the uncertainties of skin temperature measurement over a wide range of environmental temperatures.

Inouye, Glickman & Keeton (114) have discussed the important problem of the evaporation of moisture through the clothing. Extending Büttner's ideas they have demonstrated that the laws of heat conduction through layers of insulation can be applied to the escape of moisture from the skin.

A basic study of the heat loss and production in cats at different temperatures has been carried out by Prouty (115). He has found that vasomotor activity is relatively unimportant in cats, and in environments of 39°C. and higher, the cat cannot prevent a rise in body temperature. On the cold side, heat production is increased with lower temperatures to keep pace with heat loss, but if the shaved cat is kept for 24 hr. at 10°C., a sharp drop in body temperature will occur. On the basis of the experiments, Prouty questions the usefulness of cats as experimental animals in the study of many of the details of heat regulation.

Brobeck (116) has observed the food intake of rats over a range of environmental temperatures from 65°F. to 97°F. At 70°F. and 94°F. the rat's body temperature was 1°F. higher than at the acclimatizing temperature 84°F., although the food intake was much higher at 70°F. than at 90°F. From this it was suggested that food intake served as a mechanism of temperature regulation.

Turner (117) has demonstrated a deficient temperature regulation in genetically obese yellow mice. The obesity and disturbed temperature regulation are attributed to the depression of activity of the mice resulting from a dysfunction of the hypothalamus.

As a result of work since the beginning of the war, the functional characteristics of the thermoregulatory system in man have become clearer. The central thermoregulatory apparatus located principally in the hypothalamus and possibly extending down into the medulla contains the cells of temperature regulation which are sensitive to blood temperature. Also, this center is capable of acting to produce fever or lowered body temperature, depending upon the effect of a particular chemical stimulus. The normal function of the central apparatus appears to be that of guarding against internal thermal stresses and in particular those that result from voluntary activity. Acting together with, but in many instances independently of the central apparatus is the pe-

ripheral mechanism consisting of the heat and cold sensory endings in the skin and the vasomotor, sweating and shivering reflexes which they can control. The function of the peripheral apparatus is to guard the organism against thermal threats arising in the environment, and to adjust heat loss so as to provide for a relatively constant deep internal temperature. As the functional relationships of this biological servo-mechanism become clearer, it will be possible to write down the mathematical operational functions which characterize it; but before that can be done, much more will have to be known of the temperature characteristics of the cells of the hypothalamus. Also, much additional information is required in regard to the sensations of heat and cold which arise in the skin.

## LITERATURE CITED

1. BENZINGER, T. H., AND KITZINGER, C., *Naval Med. Research Inst., Project NM 000 003, Report No. 1* (Jan. 6, 1949)
2. BENZINGER, T. H., AND KITZINGER, C., *Naval Med. Research Inst., Project NM 001-111, Report No. 1* (May 4, 1948)
3. SPOOR, H. J., *J. Applied Physiol.*, **1**, 369 (1948)
4. HUNTER, J. A., STACY, R. W., AND HITCHCOCK, F. A., *Rev. Sci. Instruments*, **20**, 333 (1949)
5. PROUTY, L. R., BARRETT, M. J., AND HARDY, J. D., *Federation Proc.*, **7**, 96 (1948)
6. PALMES, E. D., *Armored Medical Research Laboratory, Project #55-1* (Ft. Knox, Ky., 1947); *Federation Proc.*, **6**, 175 (1947)
7. PALMES, E. D., AND PARK, C. R., *Med. Dept. Field Research Lab., Project #55-3* (Ft. Knox, Ky., 1947)
8. KROGH, A., *Committee for the Study of Domestic Heating, Contrib. No. 6* (Copenhagen, 1948)
9. PEDERSON, L., *Committee for the Study of Domestic Heating, Contrib. No. 2* (Copenhagen, 1948)
10. RICHARDS, C. H., AND HARDY, J. D., *Federation Proc.*, **7**, 102 (1948)
11. RICHARDS, C. H., AND HARDY, J. D., *Federation Proc.*, **8**, 131 (1949)
12. HERRICK, J. F., AND GLARBORG, E., *Federation Proc.*, **8**, 73 (1949)
13. PALMES, E. D., AND PARK, C. R., *Federation Proc.*, **6**, 175 (1947)
14. HENRIQUES, F. C., *Rev. Sci. Instruments*, **18**, 673 (1947)
15. STOLL, A. M., AND HARDY, J. D., *Federation Proc.*, **7**, 120 (1948)
16. BAZETT, H. C., LOVE, L., NEWTON, M., EISENBERG, L., DAY, R., AND FORSTER, R., 2nd, *J. Applied Physiol.*, **1**, 3 (1948)
17. HORVATH, S. M., MILLER, R. N., AND HUTT, B. K., *Federation Proc.*, **7**, 58 (1948)
18. ROBBARD, S., *Am. J. Physiol.*, **150**, 67 (1947)
19. TOLPIN, M., AND ROBBARD, S., *Federation Proc.*, **6**, 215 (1947)
20. SMITH, E. D., ERSHOFF, B. H., WINZLER, R. J., AND DEUEL, H. J., JR., *J. Nutrition*, **35**, 39 (1948)
21. SWINYARD, E. A., AND TOMAN, J. E. P., *Am. J. Physiol.*, **154**, 207 (1948)
22. ELLIOTT, H. W., AND CRISMON, J. M., *Am. J. Physiol.*, **151**, 366 (1947)

23. CHATFIELD, P. O., BATTISTA, A. F., LYMAN, C. P., AND GARCIA, J. P., *Am. J. Physiol.*, **155**, 179 (1948)
24. CHANG, M. C., *J. Gen. Physiol.*, **31**, 385 (1947-48)
25. PATT, H. M., AND SWIFT, M. N., *Am. J. Physiol.*, **155**, 388 (1948)
26. FAIRFIELD, J., *Am. J. Physiol.*, **155**, 355 (1948)
27. STULLKEN, D. E., WHITE, F. M., AND HIESTAND, W. A., *Federation Proc.*, **8**, 152 (1949)
28. ADOLPH, E. F., *Am. J. Physiol.*, **155**, 366 (1948); *Federation Proc.*, **7**, 1 (1948)
29. ADOLPH, E. F., *Am. J. Physiol.*, **155**, 379 (1948); *Federation Proc.*, **7**, 1 (1948)
30. GOSSELIN, R. E., *Federation Proc.*, **7**, 42 (1948)
31. HATERIUS, H. O., AND MAISON, G. L., *Am. J. Physiol.*, **152**, 225 (1948); *Federation Proc.*, **6**, 124 (1947)
32. HEGNAUER, A. H., AND HATERIUS, H. O., *Federation Proc.*, **8**, 71 (1949)
33. ROSENHAIN, F. R., AND PENROD, K. E., *Federation Proc.*, **8**, 134 (1949)
34. HATERIUS, H. O., AND HEGNAUER, A. H., *Federation Proc.*, **8**, 69 (1949)
35. HEGNAUER, A. H., *Federation Proc.*, **8**, 71 (1949)
36. HORVATH, S. M., FOLK, G. E., CRAIG, F. N., AND FLEISCHMANN, W., *Science*, **107**, 171 (1948)
37. STREICHER, E., HACKEL, D. B., FLEISCHMANN, W., AND BYLGER, G. L., *Federation Proc.*, **8**, 151 (1949)
38. THEREIN, M., AND DUGAL, L. P., *Federation Proc.*, **8**, 156 (1949)
39. PERKINS, J. F., JR., AND NICHOLAS, C. H., *Federation Proc.*, **8**, 126 (1949)
40. HORVATH, S. M., FRIEDMAN, A., AND GOLDEN, H., *Federation Proc.*, **6**, 133 (1947); *Am. J. Physiol.*, **150**, 99 (1947)
41. JOHNSON, R. E., AND KARK, R. M., *Federation Proc.*, **6**, 138 (1947)
42. FRANTZ, J. A., AND ROTH, J. L. A., *Federation Proc.*, **7**, 35 (1948)
43. DONHOFFER, S., AND VONOTZKY, J., *Am. J. Physiol.*, **150**, 329 (1947)
44. SPEALMAN, C. R., YAMAMATO, W., BIXBY, E. W., AND NEWTON, M., *Am. J. Physiol.*, **152**, 233 (1948)
45. HORVATH, S. M., *Am. J. Physiol.*, **152**, 242 (1948)
46. BADER, R. E., ELIOT, J. W., AND BASS, D. E., *Federation Proc.*, **8**, 7 (1949)
47. TUTTLE, W. W., HAPF, W. P., AND WILSON, M., *Federation Proc.*, **8**, 167 (1949)
48. HORVATH, S. M., AND BOTELO, S. Y., *J. Applied Physiol.*, **1**, 586 (1948)
49. RAPAPORT, S. I., FETCHER, E. S., AND HALL, J. F., *Federation Proc.*, **7**, 99 (1948)
50. FETCHER, E. S., RAPAPORT, S. I., AND HALL, J. F., *Federation Proc.*, **7**, 33 (1948)
51. KROGH, A., *Committee for the Study of Domestic Heating, Contrib. No. 6* (Copenhagen, 1948)
52. AMES, A., GRIFFITH, R. S., GOLDTHWAIT, D. A., MACHT, M. B., AND BELDING, H. S., *Federation Proc.*, **7**, 2 (1948)
53. BLOCKLEY, W. V., AND TAYLOR, C. L., *Air Materiel Command, Wright-Patterson Air Force Base, Memorandum Rept. MCREXD 696-113A* (1948)
54. ADOLPH, E. F., *Physiology of Man in the Desert*, 357 pp. (Interscience Publishers, Inc., New York, 1947)
55. STEIN, H. J., ELIOT, J. W., AND BADER, R. A., *J. Applied Physiol.*, **1**, 575 (1949)
56. GALVÃO, P. E., *J. Applied Physiol.*, **1**, 385 (1948)

57. GALVÃO, P. E., *J. Applied Physiol.*, **1**, 395 (1948)
58. HARDY, J. D., SHORR, E., AND DU BOIS, E. F., *Federation Proc.*, **6**, 122 (1947)
59. THOMPSON, E. M., COX, E. W., AND RIDGWAY, A. M., *J. Nutrition*, **36**, 507 (1948)
60. LEE, D. H. K., AND MACPHERSON, R. K., *J. Applied Physiol.*, **1**, 60 (1948)
61. LADELL, W. S. S., *J. Physiol. (London)*, **106**, 237 (1947)
62. LADELL, W. S. S., *J. Physiol. London*, **107**, 465 (1948)
63. HIESTAND, W. S., AND FULLER, F. D., *Federation Proc.*, **7**, 54 (1948)
64. ROBBARD, S., AND FINK, A., *Am. J. Physiol.*, **152**, 383 (1948)
65. GIESE, A. C., AND HEATH, H. D., *J. General Physiol.*, **31**, 249 (1947-48)
66. BAZETT, H. C., MENDELSON, E. S., LOVE, L., AND LIBET, B., *J. Applied Physiol.*, **1**, 169 (1948)
67. BAZETT, H. C., LOVE, L., MENDELSON, E. S., AND PETERSON, L. H., *Federation Proc.*, **6**, 76 (1947)
68. EISENBERG, L., AND BAZETT, H. C., *Federation Proc.*, **7**, 30 (1948)
69. EICHNA, L. W., BERGER, A. R., AND RADER, B., *Federation Proc.*, **8**, 40 (1949)
70. HORVATH, S. M., FOLTZ, E. L., RUBIN, A., AND HUTT, B. K., *Federation Proc.*, **8**, 77 (1949)
71. PENNES, H. H., *J. Applied Physiol.*, **1**, 93 (1948)
72. YAGLOU, C. P., AND CONSOLAZIO, W. V., Project X-205, Rept. No. 8 (Sept. 2, 1947), Naval Med. Research Inst., Bethesda, Md., in *Bu. Med. News Letter*, **10**, 16 (1947)
73. NIMS, L. F., KARTIN, B., CHERNOFF, H. M., AND NAHUM, L. H., *Federation Proc.*, **7**, 86 (1948)
74. ROBBARD, S., TAYLOR, L., AND FERGUSON, D., *Federation Proc.*, **8**, 133 (1949)
75. BADER, M. E., AND MACHT, M. B., *J. Applied Physiol.*, **1**, 215 (1948)
- 75a. HARDY, J. D., AND OPPEL, T. M., *J. Clin. Invest.*, **16**, 533 (1937)
76. FETCHER, E. S., HALL, J. F., AND SHAUB, H. G., *Air Materiel Command, Memorandum Rep. No. MCREXD-696-113S* (1949)
77. BELDING, H. S., MEAD, J., AND BADER, M. E., *Federation Proc.*, **8**, 9 (1949)
78. SMITH, D. E., RANDALL, W. C., AND HERTZMAN, A. B., *Federation Proc.*, **7**, 116 (1948)
79. FERRIS, B. G., JR., FORSTER, R. E., 2nd, PILLION, E. L., AND CHRISTENSEN, W. R., *Am. J. Physiol.*, **150**, 304 (1947); *Federation Proc.*, **6**, 102 (1947)
80. BADER, M. E., AND MEAD, J., *Federation Proc.*, **8**, 6 (1949)
81. KERSLAKE, D. M., AND COOPER, K. E., *Royal Air Force Institute of Aviation Medicine, Rep. No. FPRC716* (1949)
82. PERKINS, J. F., LI, MAO-C., HOFFMAN, F., AND HOFFMAN, E., *Am. J. Physiol.*, **155**, 165 (1948)
83. KEMP, C. R., TUTTLE, W. W., AND HINES, H. M., *Am. J. Physiol.*, **150**, 705 (1947)
84. EBAUGH, F. G., AND THAUER, R., *Federation Proc.*, **8**, 38 (1949)
85. NIELSEN, M., *Committee for the Study of Domestic Heating, Contrib. No. 4* (Copenhagen, 1948)
86. BØJE, O., NIELSEN, M., AND OLESEN, J., *Committee for the Study of Domestic Heating, Contrib. No. 9* (Copenhagen, 1948)
87. NIELSEN, M., *Committee for the Study of Domestic Heating, Contrib. No. 3* (Copenhagen, 1947)
88. MACHT, M. B., *Federation Proc.*, **6**, 161 (1947)

89. KELLER, A. D., *Am. J. Physiol.*, **154**, 82 (1948)
90. CHAMBERS, W. W., AND WINDLE, W. F., *Federation Proc.*, **6**, 89 (1947)
91. DELGADO, J. M. R., AND LIVINGSTON, R. B., *J. Neurophysiol.*, **11**, 39 (1948)
92. BUCHANAN, A. R., AND HILL, R. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 602 (1947)
93. RODBARD, S., *Federation Proc.*, **6**, 191 (1947)
94. RODBARD, S., *Federation Proc.*, **6**, 191 (1947)
95. HALL, V. E., FIELD, J., AND GRANT, R., *Air Materiel Command, Wright-Patterson Air Force Base, Memorandum Report MCREXD-696-113D* (1948)
96. HALL, V. E., GRANT, R., AND FIELD, J., *Federation Proc.*, **7**, 48 (1948)
97. FIELD, J., PEISS, C. N., AND HALL, V. E., *Federation Proc.*, **7**, 33 (1948)
98. GRANT, R., AND ROBBINS, M. E., *Federation Proc.*, **8**, 59 (1949)
99. HEAGY, F. C., AND BURTON, A. C., *Am. J. Physiol.*, **152**, 407-16 (1948)
100. ASMUSSEN, E., AND NIELSEN, M., *Acta Physiol. Scand.*, **14**, 373 (1947)
101. ROBINSON, S., *Federation Proc.*, **6**, 190 (1947)
102. PARK, C. R., AND PALMES, E. D., *Medical Department, Field Research Lab. Project No. 2-17-1* (Ft. Knox, Ky., 1947)
103. PARK, C. R., AND PALMES, E. D., *Medical Department, Field Research Lab. Project No. 6-64-12-06* (Ft. Knox, Ky., 1948)
104. WELLS, J. S., AND RALL, D. P., *Proc. Soc. Exptl. Biol. Med.*, **68**, 421 (1948)
105. HEMINGWAY, A., *Federation Proc.*, **6**, 128 (1947)
106. KOTTKE, F. J., PHALEN, J. S., TAYLOR, C. B., VISSCHER, M. B., AND EVANS, G. T., *Am. J. Physiol.*, **153**, 10 (1948)
107. HARDY, J. D., AND GOODELL, H., *Federation Proc.*, **6**, 122 (1947)
108. BURCH, G. E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 521 (1948)
109. RANDALL, W. C., DEERING, R., AND DOUGHERTY, I., *J. Applied Physiol.*, **1**, 53 (1948)
110. MOLE, R. H., *J. Physiol. London*, **107**, 399 (1948)
111. ALBERT, R. E., AND PALMES, E. D., *Federation Proc.*, **8**, 1 (1949)
112. FRANKE, F. E., RANDALL, W. C., SMITH, D. E., AND HERTZMAN, A. B., *Federation Proc.*, **6**, 105 (1947)
113. LOVE, L. H., *J. Applied Physiol.*, **1**, 120 (1948)
114. INOUE, T., GLICKMAN, N., AND KEETON, R. W., *Federation Proc.*, **8**, 80 (1949)
115. PROUTY, L. R., *Federation Proc.*, **8**, 128 (1949)
116. BROBECK, J. R., *Federation Proc.*, **7**, 13 (1948)
117. TURNER, M. L., *Am. J. Physiol.*, **152**, 197 (1948)
118. GAGGE, A. P., *Am. J. Physiol.*, **120**, 277 (1937)
119. BÜTTNER, K., *Biol. Zentr.*, **55**, 356 (1935)

## WATER METABOLISM

By J. RUSSELL ELKINTON<sup>1</sup>

*Department of Medicine, University of Pennsylvania School of Medicine,  
Philadelphia, Pennsylvania*

The emphasis of study in the field of water and electrolyte metabolism has altered distinctly during the past few years. Investigators have turned from problems of military import, such as the study of physiological stresses associated with extremes of temperature, with deprivation of water, and with trauma. Advances in these fields have been reviewed in previous volumes (1, 2) and in monographs (3). During the period of this review (July 1947 to June 1949) the chief endeavors in this field have been directed toward elucidation of physiological processes in normal organisms and their distortions due to disease. Outstanding work has been done especially in regard to (a) the mechanism of renal excretion of water and electrolytes, (b) the relation of retention of water and electrolytes to cardiovascular disturbances (cardiac edema), and (c) the distortion and deficiencies of intracellular fluid in various pathological conditions. These studies have been aided materially by the development of reliable methods of flame photometry for rapid determination of sodium and potassium ions (4), and by the availability of radioactive isotopes.

The ubiquitous distribution of water in the body and the close association of its transfers with those of its principal ionic solutes, precludes their separate consideration. Only those investigations will be reviewed in which exchanges of these solutes pertain to the exchanges of the solvent, water, between the several phases of body fluids, and between the body as a whole and the environment.

### DISTRIBUTION OF WATER WITHIN THE BODY

*Mechanisms of osmotic transfers.*—Since living membranes have been found in general to be freely permeable to water, transfers of water across phase boundaries are dependent upon the osmotic forces exerted by the solutes of the respective phases. Consideration is pertinent, therefore, of the factors which determine the

<sup>1</sup> Established Investigator of the American Heart Association.

osmotic pressures of solutes in various systems. Urea being completely diffusible and glucose at least partially diffusible between extracellular and intracellular fluid, the distribution of water between these two phases depends primarily upon their respective concentration of dissociated electrolytes. Various hypotheses concerning the differential distribution of the principal cations, sodium and potassium, have been tested and discussed.

In his excellent review of the transport of ions across cellular membranes, Ussing (5) states that the processes by which an ion crosses a membrane are diffusion, exchange diffusion, or active transport. Diffusion takes place when the electrochemical potentials of an ion differ on two sides of a membrane permeable to the ion. Exchange diffusion, a term introduced by Ussing (6, 7), indicates an ion species crossing a membrane in both directions by temporary combination with a carrier molecule which cannot leave the membrane. The involvement of a carrier system is similar to active transport, but differs in that no energy is used and a net transport of the ion is not affected. Active transport is the transfer of ions from a lower to a higher electrochemical potential and involves expenditure of energy. Ussing (5) points out that the first two processes cannot explain many of the ion distributions found, and that much has yet to be learned concerning the many specific metabolic processes involved in the active transport of ions.

Several theoretical models of such active ionic transports have been set up. Franck & Mayer (8) have postulated a cellular system in which catalytic transformation of substance *a* to *b* takes place at one end of a cell and the reverse reaction of *b* to *a* takes place at the other end of the cell. Driven by energy from another chemical reaction and given different diffusion coefficients, active transport of *a*, *b*, or the solvent may take place. Such a system is thermodynamically efficient as the ratio of expended free energy to that given to the transported material may be as low as three. Rosenberg (9), in a thermodynamic treatment of active ion transport excludes all forces but chemical potentials as responsible for active transport processes. Osterhout (10, 11, 12), from observations of the movement of water through the *Nitella* cell containing sucrose at one end, has postulated that if inequalities of osmotic pressure occur because of metabolic processes, the secreting cell can take up water at one portion of its surface and expel it at another.

It is apparent that energy producing reactions are necessary to the transfer of ions across the cell boundary and to the maintenance of their differential distribution. Boyle & Conway (13) originally hypothesized that the differential could be explained as a Donnan phenomenon due to the nondiffusibility of intracellular anions and extracellular sodium, the nondiffusibility of these ions resulting from their greater ionic diameter. Definite evidence of the existence of sodium within cells, however, led Dean (14) to postulate the active extrusion of sodium; and Conway (15) has now accepted this as a necessary corollary to his theory. Conway & Hingerty (16) studied the exchanges of sodium and potassium in mammalian muscle during potassium administration to rats previously deprived of the ion. The release of cellular sodium was much slower than the uptake of potassium, the half-period of extrusion of sodium being about three days. They concluded that the extrusion of sodium must be an active process, and that there was no simple competition between cellular sodium and potassium for anions. Levi & Ussing (17), using radioactive sodium, have confirmed the active transport of intracellular sodium. In the isolated frog sartorius, the half-renewal rate of the sodium of the muscle fiber was found to be as fast as 30 min. It was concluded that active transport was probably involved, although the rate was so high for the energy involved that the process of exchange diffusion must have been taking place as well. In another study of the exchange of  $\text{Na}^{24}$  across the isolated frog skin,  $\text{Na}^{24}$  was extruded against a concentration gradient except when the system was poisoned with cyanide (7). This was further evidence that the exchange was driven by the energy of oxidative processes.

Although Ussing in his review (5) states that there is little evidence for the active transport of potassium into muscle fibers, the maintenance of the equilibrium appears to depend at least indirectly upon active or energy-producing reactions within the cell. This point of view fits in well with previous evidence that transport of potassium across cell boundaries is closely linked with metabolic processes, especially the carbohydrate phosphorylation cycle, and is supported by further current studies. Muntz (18) found that potassium or ammonium ions were essential to the fermentation of glucose to hexose diphosphate in dialyzed yeast maceration juice, and Schmidt *et al.* (19) demonstrated that potassium ion

was necessary to the formation of metaphosphate by bakers yeast. Dixon (20) studied the anaerobic metabolism of slices of cerebral cortex. In the presence of glucose there was no leakage of potassium from the tissue, and potassium was sometimes taken up from the perfusing fluid; in the absence of glucose or when glycolysis was inhibited by fluoride, potassium left the cells. These findings were confirmed by Krebs & Eggleston (21) who showed that the addition of L-glutamate, the only amino acid readily oxidized in the brain, further promoted the retention of potassium by the tissues.

These studies link the uptake of potassium to metabolic processes within the cells, but do not exclude the possibility that such uptake is mediated through the active extrusion of sodium. Nevertheless, it is difficult to accept this latter concept in face of the evidence that exchange of intracellular sodium and potassium may bear very little relation to each other [Conway & Hingerty (16)]. Elkinton, Winkler & Danowski (22), in analyzing the exchanges of these two electrolytes in a variety of clinical and experimental studies, found only occasional reciprocal relationships between the two; and data on the transfers of cellular sodium during the uptake of administered potassium in cases of potassium deficiency due to infant diarrhea (23) and diabetic acidosis (24) confirm this observation. Elkinton *et al.* (22) also found that administered potassium was not distributed between the extracellular and intracellular phases in proportion to their respective volumes, an observation repeatedly confirmed in more recent studies of potassium therapy (24, 25). Yet such would be the expectation from the Conway theory.

Osmotic shift of water between extracellular and intracellular fluids depends not only on transfers of ions across the cell boundary but also on changes in osmotic activity of solutes within the cell. While the major portion of intracellular potassium is free or ionized evidence has accumulated that some of it is bound (5, 26). That potassium may be accumulated in inactive form within the cell is recognized by Conway (15), who points out that the cellular constituents to which it is bound must vary as the result of growth and metabolism. Demonstration of changes in this portion of intracellular base is difficult, but evidence is strong that such changes do take place. Elkinton, Winkler & Danowski (22), in the analysis of balance experiments mentioned above, were unable

to correlate the calculated changes in osmotically active cell base with the net exchanges of cell sodium plus potassium or with any particular experimental conditions. Nevertheless, the magnitude of the former could exceed that of the latter, and hence this phenomenon must be taken into consideration in any discussion of osmotic transfers of water. Factors which control such changes are completely unknown. Such a change, for instance, has been demonstrated by Shapiro (27) to occur when the egg of the sea urchin, *Arbacia punctulata*, has been fertilized. Opie (28) has presented an extensive study of the rate of uptake of water and salt solutions of various tissues following removal from the body. The rate of uptake varied with time and the concentration of the surrounding medium, and different tissues appeared to have different isosmotic levels. While their findings were *in vitro* studies, they nevertheless suggest disparities between tissues of cellular osmotic pressures, disparities that conceivably are present during life and are conditioned by metabolic processes.

Wolf (29) has formulated an ingenious equation to describe changes in the extracellular fluid volume that may be predicted if the body is a perfect osmometer. Where  $V_e$  and  $V'_e$  are the initial and final volumes of extracellular fluid,  $A$  is the initial osmolar concentration in the body fluids,  $W$  is the initial total body water volume, and  $L_{H_2O}$  and  $L$  are the load of water and of solute in the extracellular compartment, respectively, then

$$V'_e = \frac{(W + L_{H_2O})(V_e A + L)}{WA + L}$$

The fundamental assumptions on which this equation is based are essentially that equilibrium takes place, that the solute load is confined to the extracellular space, and that no change takes place in the quantity of osmotically active intracellular solute. Application of this equation by Wolf to some of the data of Winkler, Elkinton, *et al.* indicated a fairly good agreement with values for  $V'_e$  as calculated from changes in the chloride balance, but discrepancies ranged as high as 21 per cent. This is fairly good agreement considering the evidence reviewed above which would invalidate the third assumption. The body does act as an osmometer, but alterations in intracellular osmotically active solutes must be

taken into account as well as changes in the load of extracellular solute. Since these intracellular alterations are mainly conditioned by metabolic processes, transfers of water are also so conditioned. The relationship of oxidative processes to electrolyte and water exchanges still offers a promising field of investigation.

*Measurement of phases of body fluids.*—Moore (30) has reviewed the problems inherent in such measurements with especial reference to the use of isotopes. The volume of distribution of antipyrine has been proposed as a measure of total body water by Soberman *et al.* (31). This substance was shown to be evenly distributed between water of a variety of tissues and water of plasma; the average ratio in two dogs was 1.01 and in one human 0.96, with a maximum value of 1.18 and a minimum of 0.83. The drug apparently diffuses freely into abnormal accumulations of fluid since in a series of patients with edema, ascites, and hydrothorax, the transudate:plasma ratios of antipyrine were from 0.89 to 1.11. Equilibration appears to take place between 1 and 2 hr. after intravenous injection, and urinary excretion was negligible over 4 hr. As antipyrine disappeared from the plasma at a constant average rate of 6 per cent per hr. in humans and 30 per cent in dogs, metabolism of the substance was assumed although recovery experiments were not reported. Because of this disappearance, the volume of distribution was calculated by extrapolating the logarithm of the plasma concentration to zero time. This extrapolation is the weakest point in the method, since reasonable variation in the extrapolation of the curves presented can produce variation in the volume calculated of as much as 2.5 l. or 10 per cent. However, using this method, the apparent volume of distribution of antipyrine in eight normal subjects ranged from 39.3 to 57.9 per cent of the body weight. Values for seven patients with abnormal water depots were larger, lying between 51.7 and 70 per cent. In these subjects total body water was measured simultaneously with deuterium oxide, with surprisingly good agreement considering the above-mentioned error of extrapolation; the average difference between the two methods was 1.2 l. for the normal, and 2.7 l. for the abnormal subjects. Since the values obtained for total body water were somewhat lower than the usually accepted range, the discrepancies were assumed to be due to variations in body fat content. In the same laboratory, Messinger & Steele (32) calcu-

lated body fat and body water from the specific gravity of nine human subjects. The results agreed well with the same values calculated from the volume of distribution of antipyrine in the same subject. The data confirm that, because of variable fat contents, total body water is more constantly related to "lean body mass" than to total body weight. The validity of antipyrine as a measure of total body water received further support from the experiments of Soberman (33), who found that the maximum difference between this method and measurement by desiccation in four rabbits was 2.9 per cent of the body weight.

The measurement of extracellular fluid volume has continued to be attempted with a variety of substances. Elkinton (34) found that the volume of distribution of mannitol following a single injection in four normal subjects ranged from 19.5 to 23.5 per cent of the body weight. Although in these experiments, in those of Clark & Barker (35), and in uremic patients (36) and nephrectomized dogs (37), mannitol appeared to be completely recovered or nonutilized, Dominguez, Corcoran & Page (38) and Berger, Farber & Earle (39) have presented data in support of the metabolism of this substance. Whether or not it is stored in cellular depots or metabolized, mannitol is not a satisfactory measure of extracellular fluid since in patients without edema abnormally large volumes have been observed (40, 41).

The use of inulin as a measure of extracellular fluid has received fresh and less equivocal support. Gaudino, Schwartz & Levitt (42), employing the constant infusion technique to attain equilibrium, obtained values in dogs of 20.9 to 23.2 per cent of body weight. The inulin space was constantly smaller than the simultaneously measured thiocyanate, radioactive sodium, or bromide spaces. In three human subjects the inulin space was 15.0 to 16.0 per cent of the body weight and smaller than the thiocyanate space. In dogs and men, 99 to 102 per cent of the inulin was recovered; and in one anuric patient, the inulin space did not expand during a period of 20 hr. Gaudino & Levitt (43) confirmed these findings in another set of experiments in dogs in which a correction was made for inulin in the dead space of the urinary tract. The average values for inulin, radioactive sodium, and thiocyanate spaces were 19.4, 30.4 and 33.8 per cent, respectively. In the study of Fellers *et al.* (44), *vide infra*, comparable results were

obtained. In four subjects the volumes of distribution of inulin, mannitol, radioactive sodium, and thiocyanate were measured; in two subjects the inulin space was lowest, and in the others it was felt that inulin was not completely recovered from the urine. In two dogs with ligated renal pedicles, the inulin space remained constant, but the mannitol space expanded.

The radioactive isotopes of sodium and chloride, thiocyanate, and bromide have continued to be used to measure "extracellular fluid," despite the previous evidence that these substances do not have identical volumes of distribution (45, 46). Wang (47), in a study of the exchanges of  $\text{Na}^{24}$  and  $\text{Cl}^{38}$  between plasma, cerebrospinal fluid, and aqueous humor of dogs, calculated the sodium and chloride spaces to be  $33 \pm 5$  per cent of the body weight, but these values have little validity because the isotopic excretions were not measured. Cope & Moore (48) determined the radioactive sodium and thiocyanate spaces in severely burned patients during therapy. During the early stages the radioactive sodium space exceeded the thiocyanate space, later the relative magnitudes were reversed; both measurements indicated overexpansion of the extracellular fluid as the chief disorder of body fluids in this condition. Ferraro *et al.* (197) found the bromide space to be expanded in cardiac failure and cirrhosis.

Changes in volume of extracellular fluid in relation to growth have been the subject of a number of investigations. Fellers *et al.* (44) determined the volumes of distribution of radioactive sodium and thiocyanate in 36 subjects from the neonatal period to adulthood. Extracellular fluid as measured by both of these methods decreased relative to total body weight as age advanced, infants having relative volumes 57 to 78 per cent greater than adults. In a few of these subjects, the inulin space was found to be smaller than the spaces of radioactive sodium and thiocyanate (*vide supra*). Other investigators have obtained similar results. Morse, Cassels & Schultz (49) determined the thiocyanate space in 65 subjects ranging in age from 3 to 17 yr., and found that the space was most consistently related to area of body surface; in terms of body weight, the space was unchanged as age increased but interstitial fluid decreased. Doxiadis & Gairdner (50) studied the volume of distribution of thiocyanate in children and adults, making a correction in their calculations for the thiocyanate bound to serum

protein. Since in normal adult subjects, repeated determinations varied by as much as 15 per cent and thiocyanate space in three obviously dehydrated infants lay within normal limits, these workers concluded that the determination of the thiocyanate space as a measure of extracellular fluid was not readily applicable to clinical problems. These data are further evidence of the unpredictable entry of thiocyanate into cells. The relation to growth in rats of plasma volume as measured by Evan's blue dye and of thiocyanate space was investigated by Wang & Hegsted (51), who found that before puberty the blue dye and thiocyanate spaces increased at a less rapid rate than the total body weight, and that the ratio of the latter to the former decreased during the entire period of growth.

Hollander, Chang & CoTui (52) used deuterium oxide and thiocyanate to study the partition of body fluids in two normal subjects and four subjects depleted of protein. In the normal subjects, the volumes of distribution of both substances, in per cent of the body weight, were 54.9 to 58.5 and 23.8 to 29.1 per cent, respectively; in the protein depleted subjects, the corresponding values were 65.8 to 76.4 and 41.0 to 46.3 per cent, respectively. Calculating intracellular fluid volume as the difference between the two measured spaces, the ratios of the intracellular fluid to total body solids were higher in the protein depleted subjects than in the normal, indicating overhydration of the intracellular as well as the extracellular phase. Using thiocyanate other workers, Henschel *et al.* (53) and Kerpel-Fronius & Kovach (54), have found evidence of relative expansion of extracellular fluid in chronic malnutrition, while Gollan (55) found no significant change. Ling & Spring (56) and Overman, Hill & Wong (57) found such large volumes of distribution of thiocyanate in patients with chronic wound infections and in patients with malaria, respectively, that extensive penetration of thiocyanate into cells in these conditions, was postulated. Expansions of the thiocyanate space have also been found in postoperative states (58), in pre-eclampsia and eclampsia (59), and in anorexia nervosa (60).

Intracellular fluid volume has been measured in the whole organism as the difference between the volumes of distribution of thiocyanate and deuterium oxide by Hollander, Chang & CoTui (52) (*vide supra*) and between those of thiocyanate and sulfanila-

mide by Painter, Holmes & Gregersen (61) (*vide infra*). Changes in intracellular fluid volume have been calculated from weight changes, metabolic and electrolyte balances (23, 62, 63, 64), and by tissue analyses (65 to 68); these investigations will be discussed below under DEPLETION OF WATER AND ELECTROLYTES AND EDEMA.

#### EXCHANGES OF WATER WITH THE ENVIRONMENT

*Transfers of water in the skin, lungs, and gastrointestinal tract.*—Relatively little work has been reported during the two years covered by this review on the exchanges of water through the skin, lungs, and gastrointestinal tract. Mole (69) has studied the factors determining the relative humidity of the skin ( $rh_s$ ) namely, the rate of diffusion of water through the skin, the skin temperature, the vapor pressure of the water in the environment, and air movement. At constant air humidity,  $rh_s$  increases in a linear manner with air temperature up to 32°C., when sweating starts; at constant air temperature,  $rh_s$  increases with air humidity. Increased relative humidity of the skin accounts for excessive water evaporation at high humidities with relatively low air temperatures. Marshall & Specht (70) observed the respiratory water vapor in 15 subjects at a simulated altitude of 30,000 ft.: the respiratory water loss decreased in proportion to the decrease in gas volume exhaled. D'Alton, Darling & Shea (71) measured the insensible water loss in eight patients with congestive heart failure (in three before and after recompensation). Insensible perspiration of the skin did not change with the circulatory status; insensible water loss from the lungs followed the changes in pulmonary ventilation. Schmidt-Nielsen (72) found that one of the adaptive mechanisms to dry environment of desert rodents of the family *Heteromyidae* is a rate of insensible water loss less than one-half that of other rodents of the same size.

The loss of electrolytes with water in sweat has been investigated under various conditions. Pratt, Cooke & Darrow (73) compared the losses of chloride, sodium, and potassium from the skin of normal infants exposed to temperatures of 80°F. and 90°F. respectively, the increases being from four to six fold. Similar losses in infants dehydrated by diarrhea (62) are discussed below. Ladell (74) has measured chloride losses in the sweat of normal

adults and has clearly delineated the changes in body fluids resulting from the loss of water and electrolytes in experimental heavy sweating (75) (*vide infra*). Evidence that the concentrations of chloride and sodium in sweat are directly controlled by the adrenal cortex has been presented by Conn and co-workers (76, 77). These workers found that the range of concentration of chloride and sodium was 12 to 60 m. eq. per l. in 21 normal subjects. In eight patients with Addison's disease the corresponding concentrations were 90 to 125 m. eq. per l. In three patients with Cushing's syndrome and two patients with adrenogenital syndrome the values were 2 to 14 m. eq. per l. These data indicate that the cells of the sweat gland tubules are analogous in this respect to those of the renal tubule, and that the determination of sweat electrolyte concentration may be a useful adjunct to methods for determining the functional state of the adrenal cortex.

*Excretion of water by the kidneys.*—The regulation by the kidney of volume and composition of body fluids has been extensively investigated. Several reviewers (78, 79, 80) have stressed the complexity of the various physiological mechanisms involved and their multitudinous interrelationships. It is generally accepted that the hormonal control of renal water excretion by the kidney is vested in the posterior pituitary gland and that of electrolyte excretion in the adrenal cortex, but the means whereby these glands are appraised of the needs for adjustment of body fluids are not entirely clarified. Moreover, the excretion of water and the excretion of solutes condition one another. Thus, a series of reactions may take place in any given adjustment of the internal environment.

Verney (81) in a Croonian lecture, has clearly elucidated the manner in which the posterior pituitary gland is stimulated to produce antidiuretic hormone for the regulation of water excretion. Using water diuresis as a standard test procedure, Verney established that the production of antidiuretic hormone could be stimulated by both neural and humoral mechanisms. Removal of the posterior pituitary or the injection of epinephrine or tyramine blocked the emotional release of antidiuretic substance induced by the stimulus of a faradic current. The epinephrine block appeared to be due to specific interference in the chain of chemical reactions initiated in the nervous system rather than to specific

effects on the cerebral or general circulation. In addition to a purely neural stimulation of the posterior pituitary gland, Verney gave strong evidence for a mechanism of osmotic stimulation. By a series of ingenious experiments, he demonstrated the presence of "osmoreceptors" in an area fed by the internal carotid artery. These structures are probably present in the supraoptic nuclei and stimulate the posterior pituitary through the supraoptico-hypophyseal tract. These osmoreceptors were very sensitive to changes in the osmotic pressure of the plasma or interstitial fluid perfusing them. Intracarotid injections of hypertonic sodium chloride, sodium sulphate, and sucrose produced the release of antidiuretic hormone; hypertonic solutions of dextrose were less effective, and such solutions of urea produced no effect. These findings would be expected from the relative cell penetration by the substances involved; sodium chloride, the least penetrating, produced the greatest osmotic effect (shift of water). Quantitation of responses to hypertonic solutions established that changes in the osmotic pressure of the order of one per cent produced a 90 per cent reduction of the maximal rate of water excretion. The osmoreceptors, therefore, are extremely sensitive to changes in the osmotic pressure of the internal environment and especially to changes in concentration of sodium ion.

The osmotic stimulation of posterior pituitary activity is probably a primary mode of regulation of water excretion under ordinary circumstances. Increased production of antidiuretic hormone has been reported in many conditions, and it is not always clear whether it is a primary reaction or a secondary response to some other distortion of the body fluid equilibria. Antidiuretic substances have been demonstrated in the urine of patients with portal cirrhosis (82), and in the urine of rats with experimentally produced liver damage (82, 83). Watson & Greenberg (84) postulated an increased production of antidiuretic hormone in four of six patients with liver disease who showed no improvement of their ascites following the injection of concentrated salt-poor albumin. However, Peters (78) described the successful delivery of ascitic fluid in a nephrotic patient by the use of this substance, and pointed out that the production of antidiuretic hormone in patients with edema due to a variety of conditions may be secondary to altered internal osmotic relationships (*vide infra*). This may be equally true re-

garding the reports of increased antidiuretic substance found in patients with cardiovascular disease (85, 86). Bader, Eliot & Bass (87) have reported that cold inhibits posterior pituitary hormone production; and Strauss, Rosenbaum & Nelson (88) gave evidence of a similar effect following whiskey ingestion, since the glomerular filtration rate was unchanged in either condition. Walker (89) reported that smoking and nicotine injected intravenously stimulated the production of antidiuretic hormone. Walker found no such effect with morphine in normal subjects, but Ferrer & Sokoloff (90) reported that morphine and demerol appeared to inhibit water diuresis in five of nine patients with congestive heart failure.

While the posterior pituitary exercises the hormonal regulation of water excretion by the kidney, the excretion of sodium and potassium is at least in part regulated by the adrenal cortex. Since excretion of sodium many have a direct effect on the excretion of water, the latter is also influenced by adrenal cortical activity. Studies in the past have shown that adrenocortical extracts and synthetic desoxycorticosterone acetate (DOCA) promote the retention of sodium and water. Recent investigations of the effects of adrenocorticotrophic hormone in normal subjects indicate equivocal results in regard to the effects of endogenous adrenal steroids on sodium and water excretion. Forsham *et al.* (91, 92) reported a definite decrease in excretion of sodium and water in human subjects, a finding corroborated by the author and colleagues in patients with certain collagen diseases (93). Other workers have found both decreases and increases (94, 95), or no change (96, 97), in sodium excretion. Because in patients with Addison's disease cortisone (11-dehydro-17-hydroxy-corticosterone or Compound E) caused diminished sodium excretion when given alone, but increased sodium excretion when given with desoxycorticosterone, Forsham *et al.* (98) postulated that various adrenal cortical steroids may have competitive or antagonistic effects on the transfers of electrolytes by the renal tubule. Although these relationships are not clear at present, there is no doubt that adrenal cortical hormones play a role in regulating the renal excretion of electrolytes and therefore of water.

Synthetic DOCA has been shown in the past to promote the retention of sodium and water in adrenal cortical insufficiency.

When given to normal subjects, diuresis or "diabetes insipidus" may be produced. Peters in his review (78) has clearly delineated the difference between this phenomenon and true diabetes insipidus due to posterior pituitary insufficiency. In the latter, obligatory polyuria causes decreased body water, increased osmotic pressure, thirst, and polydipsia; in the former, sodium retention causes increased osmotic pressure, thirst, polydipsia, increased body water, and finally polyuria. This concept has received support from a number of current studies. Osborn & Eversole (99) reported that the diuretic effect of DOCA was observed in hydrated, but not in dehydrated, rats. The evidence of Lotspeich (100) and of Birnie *et al.* (101) that adrenalectomy in rats is associated with increased antidiuretic hormone production is not inconsistent. Sartorius & Roberts (102) reported that desoxycorticosterone given before pitressin to a water loaded subject inhibited the antidiuretic effect of the latter. The observations of Skahen & Green (103) appear to be less consistent with the investigations detailed above. These workers found that the administration of desoxycorticosterone to rats produced an increase in fluid intake and in urinary output of antidiuretic substance, an effect which was augmented by the ingestion of isotonic sodium chloride instead of water. It is probable that such a sequence precedes the onset of desoxycorticosterone "diabetes insipidus."

That pitressin may be antagonistic to desoxycorticosterone in that it has a direct inhibitory effect on the reabsorption of chloride and sodium in the renal tubule has been suggested by the evidence of Little *et al.* (104), Anslow *et al.* (105), and Sartorius & Roberts (102). Anslow *et al.* point out, however, that such an effect is only produced under conditions of an overload of water when the endogenous secretion of the posterior pituitary hormone is presumably minimal; there is thus no unequivocal evidence that the antidiuretic hormone is implicated in the direct control of the tubular reabsorption of chloride and sodium.

Hormonal control of the tubular reabsorption of water and solutes in the kidney is not the sole determinant of the composition of urine under conditions of physiological stress. It is generally accepted that some 80 to 85 per cent of glomerular filtrate is reabsorbed isosmotically in the proximal tubule and thin segment (106). By inducing an osmotic diuresis in dogs with mannitol,

Wesson, Anslow & Smith (107, 108) showed that the maximum rate of urine flow attainable was equivalent to 65 per cent of the water filtered, while only 27 per cent of the filtered sodium was excreted. The data suggested that sodium is actively, and water is passively reabsorbed in the proximal tubule. Cizek & Holmes (109), however, reported that in osmotic diuresis induced in dogs with sucrose, glucose, sorbitol, and urea, chloride excretion varied directly with urine volume regardless of the diuretic used. Rapoport and co-workers (110) found this to be so for sodium as well as chloride in glucose diuresis, but not in urea diuresis. Relman, Goodyer & Peterson (111) found sodium and chloride excretion to be increased in mannitol diuresis. Water diuresis, on the other hand, may be associated with a decreased rate of excretion of sodium (112). Equally conflicting evidence has been adduced in regard to the effect of excessive water excretion on potassium excretion. Rapoport *et al.* (110, 113) produced no change in rate of potassium excretion with any diuretic, a finding confirmed by Relman, Goodyer & Peterson (111) in diuresis due to mannitol, and by Seldin & Tarail (114) in diuresis due to glucose and mannitol. However, the latter workers observed the rate of potassium excretion to treble during water diuresis.

Current evidence supports the concept that excesses of solutes put a much stronger compulsion in the excretion of water than excesses of water do on the excretion of solutes. Rapoport and co-workers (110, 113, 115, 116) studied the relationships between solute excretion, urine flow, and renal osmotic work in subjects deprived of water. In hydropenic subjects with "resting" kidneys, *i.e.*, with no solute loading, maximal osmolarity ( $1,182 \pm 18$  milliosmols per l.) was observed during minimal urine flow, but the actual osmotic work performed was little more than in subjects with normal rates of flow. When the subjects were loaded with a series of solutes including glucose, sucrose, mannitol, xylose, sorbitol, creatinine, sodium *p*-aminohippurate, sodium sulphate, and sodium chloride, a constant relationship was found between the rate of solute excretion and the rate of urine flow. This was true regardless of the nature of the solute or its mode of renal excretion. The calculated ideal osmotic work value rose about 10 times to a maximum of 4.0 calories per min.; beyond this point no further work increase could be produced by increasing solute load, solute

plasma level, or urine flow. These workers pointed out that the load of solutes in tubular urine may differ greatly from the dose of solute administered because of variations in volume of distribution, manner of renal excretion, and metabolic fate.

Other observations have been made on the effect of the excretion of solutes on the excretion of water. Pratt, Bienvenu & Whyte (117) observed the maximum urine concentration of water deprived young infants to be 1,200 milliosmols per l. Smith *et al.* (118), however, determined the maximum urinary concentration of premature and newborn infants to be only 650 milliosmols per l., and McCance & Wilkinson (119) found in newborn rats that when hypertonic solutions of sodium chloride or urea were administered, the solutes could not be concentrated in the urine to the same extent as in adults. When the newborn animals were loaded with water, diuresis also failed to occur, an observation likewise made by Heller (120). The subject of renal function in early life has been completely reviewed by McCance (121), who concludes that the kidney of the newborn child or animal has relatively little flexibility and is much less able to adjust disturbances in the mutual relationships of water, sodium chloride, and urea in the internal environment.

The hypothesis that under conditions of solute loading the only determinant of urine volume and composition is the total osmotic pressure of tubular urine has been challenged by Seldin & Tarail (114). These workers found that less water and sodium was excreted following the administration of urea than following that of glucose and mannitol. Since the latter substances are less diffusible across cell membranes, water was withdrawn from cells as the osmotic pressure of extracellular fluid was elevated; therefore, the extracellular concentration of sodium fell. The conclusion was drawn that under such conditions the state of hydration of the intracellular phase and the total osmotic pressure of serum and extracellular fluid are important factors in determining the renal excretion of water and electrolytes.

*Thirst.*—In discussing the exchanges of water with the environment, the subject of thirst cannot be omitted. No evidence has been produced that completely dissociates thirst from the state of hydration of the body. Adolph (122, 123), in a series of experiments, has demonstrated in rats that a high turnover of

water (ingestion and excretion) produced by diluted foods, could be inhibited by atropine, pilocarpine, and posterior pituitary. Inhibition of thirst by pilocarpine and doryl did not correlate with the stimulation of excessive salivation. Except following posterior pituitary extracts, water diuresis could be induced by the administration of water through a stomach tube. Following partial nephrectomy, water ingestion was diminished during the temporary inability to excrete water. These studies are interpreted to indicate that water turnover is regulated by both intake and output and that factors other than the water load may be operative but are unknown. Archdeacon, Presnell & Walton (124) found in the failure of atropine to stimulate water ingestion, similar evidence that the salivary glands were not the main regulators of thirst.

#### EDEMA

Investigative interest has increased enormously in the physiological disturbances involved in edematous states and especially in edema due to cardiac failure. Several comprehensive reviews of the subject have appeared (78, 79, 125 to 134).

*Cardiac edema.*—The retention of water by patients with congestive heart failure is closely associated with the retention of sodium. Current evidence for this well-established fact is found in the studies of Burch and associates (135, 136) who demonstrated a delayed turnover and excretion of radioactive sodium in such patients, and in the work of Gorham *et al.* (137) who showed the therapeutic advantage of restriction of intake of sodium in relation to that of water. The sequence of events, however, which leads to retention of sodium and water, is not beyond dispute. In 1944 Warren & Stead (138) proposed a theory of "forward failure," strongly supported by Starr (125), to account for the edema of heart failure, with the following steps of events: decrease in cardiac output, decrease in renal blood flow, decrease in glomerular filtration, retention of sodium and then water, increase in blood volume, increase in venous and capillary hydrostatic pressure, transudation into interstitial spaces, edema. This hypothesis was based on the observation in a number of patients of weight gain before venous pressure elevation and on evidence of overexpansion of blood volume as measured by the apparent volume of distribu-

tion of Evan's blue dye; and it was supported by the report of Merrill (139) of low rates of glomerular filtration and renal plasma flow in the patients with congestive failure. The sequence of events according to the older hypothesis of failure, based on Starling's theory of fluid exchange, has been restated by Peters (78): elevation of venous and capillary hydrostatic pressure, transudation of fluid, diminished effective blood volume, retention of sodium and water by the kidney. In support of this sequence, Peters points out the reasons for questioning the validity of Evan's blue dye as a measure of plasma volume and sets forth considerable physiological evidence to indicate that dehydration and diminished plasma volume are the strongest stimuli to the kidney to retain sodium and water.

The role of the kidney in the production of edema in cardiac failure has been the subject of numerous studies. Mokotoff, Ross & Leiter (140) confirmed Merrill's (139) finding of lowered rates of glomerular filtration in patients with cardiac edema. These workers calculated a linear relationship between glomerular filtration and tubular reabsorption of sodium. They stated that, since the tubular reabsorption of sodium per unit of glomerular filtrate was the same in the cardiacs as in the normal controls, the retention of sodium was due to the diminution in glomerular filtration. Wesson, Anslow & Smith (126) have elaborated this concept of glomerulo-tubular imbalance in cardiac failure. They present evidence that there exists in the distal tubule a maximal rate of reabsorption of sodium,  $T^d_{m_{Na}}$ . Given then an obligatory and constant isosmotic reabsorption of glomerular filtrate in the proximal tubule and thin segment, they postulate that small variations in filtration rate will cause a significant variation in the relatively small portion of filtered sodium which is excreted. The demonstrated diminution in glomerular filtration, therefore, would account for the sodium retention of heart failure.

There are theoretical and experimental difficulties with this explanation of the low renal excretion of sodium in cardiac edema. The fact that 95 to 99.9 per cent of the glomerular filtrate is reabsorbed in the tubule imposes a priori a linear relationship between these two functions. Small deviations from this ratio (barely detectable) in the values given of tubular sodium reabsorbed per unit of filtrate, may make a difference of 10 gm. or more in sodium

chloride excretion in 24 hr. Furthermore the data of Mokotoff *et al.* (140) shows that the excretion rate of sodium in a cardiac with a lowered glomerular filtration rate and on a moderate intake of sodium, may exceed that of a control subject with a normal rate of glomerular filtration who is on a low intake of sodium. The relationship between glomerular filtration and sodium excretion is an inverse one under these circumstances. The hypothesis of Wesson, Anslow & Smith (126) that variations in sodium excretion are effected by variations in glomerular filtration is difficult to accept *in toto* because it rests on the basic assumption that the distal tubular maximal rate of sodium reabsorption is operative at all times. Such a maximal capacity for transfer of sodium would limit the excretion of excessive tubular loads of sodium, but if distal tubular transfers at maximal rates are operative under conditions of minimal tubular load of sodium, the term facultative reabsorption is a misnomer. The conclusion appears unavoidable that alterations in tubular reabsorption play a primary role in the diminished excretion of sodium in heart failure.

This concept is supported by the clinical studies of Borst (141) and by much experimental evidence. Delivery of edema during recompensation of decompensated cardiac patients has been shown to occur without significant increases in the glomerular filtration rate by at least four groups of workers (142 to 146). In all these studies the significant change was the increase in the fraction of filtered sodium which was rejected by the tubules. Green *et al.* (147) loaded normal dogs with sodium and observed increased sodium excretion without changes in glomerular filtration rate and in patients, with various rates of filtration but with comparable sodium loads, found a high degree of inverse correlation between the rates of filtration and excretion.

Circulatory factors which affect tubular reabsorption of electrolytes and water are being sought. Briggs *et al.* (142) reported that a decreased oxygen tension in the mixed venous blood of the right atrium was the most consistent finding in their group of decompensated patients. That anoxia in the renal tubule may affect tubular transfers, is also suggested by the study of Galdston, Berger & Horwitz (148, 149) who observed that inhalation of 14 per cent oxygen by normal subjects greatly increased the renal excretion of chloride, sodium, and water without producing signifi-

cant changes in renal plasma flow or glomerular filtration rate. Increased renal venous pressure in normal humans and dogs has been demonstrated by Bradley, Blake, and co-workers (150, 151) to decrease the renal excretion of sodium and water without great changes in renal plasma flow and glomerular filtration rate, *i.e.*, tubular reabsorption was increased; and Maxwell, Breed & Schwartz (152) measured a significant elevation of pressure in the renal vein in five patients with congestive heart failure and edema. Selkurt, Hall & Spencer (153) were unable to reduce the glomerular filtration rate to critical levels by graded obstruction to the renal vein in dogs but did not study the effect of renal venous hypertension on the excretion of sodium and water.

Hormonal influences on the renal tubular reabsorption of electrolytes and water have also been implicated in the edema of cardiac patients. Parrish (154) studied the corticoid content of the urine of 10 patients in congestive failure: increased corticoids which prolonged the life of adrenalectomized rat were found in four, and increased corticoids with glycogenic activity were found in all 10. Merrill (155) reported low concentrations of sodium in sweat [Conn (77)] in six of seven patients with severe heart failure and low glomerular filtration rates. These studies indicate that overactivity of the adrenal cortex may be involved in the etiology of cardiac edema. Bercu, Rokaw & Massie (156) reported increased antidiuretic substance in the urine of nine patients with congestive heart failure. Mokotoff *et al.* (157) found evidence of vasomotor depressor material (VDM), an antidiuretic substance, in excess of excitator material (VEM) in a number of patients with congestive failure.

The pertinent and unanswered question in the problem of edema is this: What are the stimuli which indicate to the kidney a need for change in rate of excretion of sodium and water, and how are these stimuli misinterpreted in pathological conditions characterized by edema? Such stimuli may act directly on the kidney or through other receptors such as the adrenal cortical gland, and the renal response may be through changes in glomerular filtration, more likely in tubular reabsorption, or in both. Peters (78, 79) has suggested that the nature of this stimulus may be changes in osmotic pressure of the plasma, blood volume, or even interstitial or intracellular fluid volume. He cites the experiments

of Welt & Orloff (158, 159), who showed that in normal subjects the injection of 25 per cent albumin led to a diminution of sodium excretion while four per cent albumin produced an increase in water excretion. In the former experiment, the plasma volume and the plasma osmotic pressure were both increased and the interstitial fluid volume must have been diminished; in the latter experiment the plasma osmotic pressure was not changed and the plasma volume was expanded with exogenous fluid. The retention of salt in the former might be a reaction to a decrease in interstitial fluid volume indicating dehydration, the excretion of water in the latter, a reaction to a stimulus suggesting overhydration. The administration of water, as advocated by Schemm (160), may in part promote the excretion of sodium by cancelling erroneous stimuli of the dehydration reaction. Aside from the nature of the stimuli, their modes of action are quite unknown.

A number of studies have indicated that abnormalities of intracellular fluid may be involved in the edema of cardiac failure. Newman, Kaltus *et al.* (144, 145) reported strongly positive potassium and nitrogen balances in one patient during a period of recompensation when diuresis was occurring with a negative sodium balance, an observation confirmed by the author (146). Fox, Friedburg & White (161) observed that in 27 of 30 patients with cardiac edema the serum level of sodium was below normal and that of chloride relatively increased, and that during a mercury diuresis more water, chloride, and potassium were excreted than sodium. Administration of sodium lactate and potassium acetate together prevented the reaccumulation of edema. These data were interpreted to indicate that cardiac edema may be characterized by a hypotonic overexpansion of both fluid phases, extracellular and intracellular, of the body. Farnsworth (162, 163) also found an increased ratio of chloride to sodium in the urine of cardiac patients, but in these observations, no account was taken of the ratio of chloride to sodium in the patients' intake (which included ammonium chloride). Schroeder (164, 165) and others (166, 167) have emphasized the deleterious effects on renal function of a low extracellular sodium concentration in patients with cardiovascular disease. The "low salt syndrome" is usually brought on by severe restriction of sodium, or as was also pointed out previously by Klinghoffer (168), by the excessive use of mercurial diuretics.

Collapse of the renal and peripheral circulation due to absolute or relative sodium depletion has a definite experimental basis [(63) *vide infra*]. The explanation of the apparent paradox of a relative deficiency of sodium in relation to water in a patient with an absolute excess of both sodium and water must be in failure of the circulation to maintain a homogeneous distribution of fluid between the extracellular phases of body tissues and the kidney. Where systemic sodium depletion has depressed the circulation despite the presence of localized depots of excess sodium and water, the administration of hypertonic solutions of sodium ion may be therapeutically effective in mobilizing such depots of edema (78, 165).

*Other types of edema.*—Studies of the pathological physiology of other types of edema can only be enumerated. Mankin & Lowell (169) studied osmotic factors influencing the formation of ascites in cirrhosis. Kunkel, Eisenmenger & Ahrens (170) found that ascites varied directly with sodium intake. McKee *et al.* (171) observed that a high-protein, low-salt diet minimized the development of experimental ascites produced by constriction of the inferior *vena cava* in dogs. Farnsworth & Krakusin (172) described a lowered ratio of sodium to chloride in the urine of two patients with cirrhosis. Dicker (198, 199) produced progressive nutritional hypoproteinemia in rats and determined the distribution of fluid in skeletal muscle, liver, and brain. The extracellular phase of muscle and liver expanded before the plasma osmotic pressure fell. When such animals were loaded with water in amounts equivalent to 5 per cent of the body weight, there was no expansion of the extracellular phase of muscle as compared with normal animals, and diuresis was delayed; the absorbed fluid appeared to be pooled in perirenal and retroperitoneal connective tissue.

Fox & McCune (173) found evidence of an intracellular fluid derangement in patients with nephrosis. Luetscher & Hall (174) observed that protein depletion in dogs and in nephrotic patients was associated with lowered rates of glomerular filtration and sodium excretion. Eder *et al.* (175) gave concentrated albumin to nephrotic patients producing a rise in plasma volume, a rise in glomerular filtration rate, and increased excretion of sodium and water. Burnett, Burrows & Commons (176) could find no correlation between sodium filtration, reabsorption, and excretion in

nephrotic patients loaded with sodium. The edema of toxemia of pregnancy was correlated with a 46 per cent greater excretion of urinary corticosteroids, according to Tobian (177). The edema of premature infants was studied by Smith *et al.* (118). Edematous and nonedematous premature infants were in negative balances of water and salt during the initial neonatal period of water restriction. The edematous infants continued to be so after feeding was started, although potassium was retained in excess of nitrogen. The authors interpreted the data to indicate that the loss of water from both fluid phases was an exaggeration of a normal physiological adjustment to birth.

#### DEPLETION OF WATER AND ELECTROLYTES<sup>2</sup>

*External exchanges of water in dehydration.*—Adolph (180) subjected a series of species of experimental animals to hot dry temperatures. Species varied in their rates of water loss and the degrees of heat tolerated. Dehydration through panting was copious only in the cat and dog, and in all species, evaporative water loss was unaffected by prior dehydration. In all species, explosive rises in temperature with heat stroke followed the critical point in dehydration when the fall in plasma volume produced circulatory failure. On the other hand, desert rodents, of the family *Heteromyidae*, were shown by the Schmidt-Nielsens (72, 181, 182) to have certain extreme adaptive mechanisms for their dry environment. Besides the reduced evaporative water loss mentioned previously, these rodents are able to conserve water by the renal excretion of solutes in concentrations as high as 1,000 millimols per l. of chloride and 240 gm. per l. of urea. The administration of sea water was tolerated and excreted with excessive amount of urea. The concentrating power of the kidneys of this species appears to exceed by far that of other mammals. Speakman *et al.* (183) subjected two human subjects to alternate four-day periods of hot and cold; while the energy metabolism was not affected, a small change in total body water took place. Siegel *et al.* (184) observed a rise in plasma specific gravity in water-deprived rats suggesting a diminution in plasma volume. Heller (185) compared the effects of water deprivation in adult and newborn rats. Adult rats were able to excrete urine of low volume and high concentra-

<sup>2</sup> Several reviews of this subject have appeared (178, 179).

tion of solutes, whereas newborn animals were not. Since in the latter the hematocrit value rose, the water content of muscle diminished, and the excretion of potassium diminished, it was concluded that the adaptive mechanism of the adult, which was not available to the newborn, consisted of an increased tubular reabsorption of water in the kidney and a shift of water from cells to extracellular fluid.

*Internal transfers of body fluids during experimental depletion.*—Painter, Holmes & Gregersen (61) studied the relation of changes in various body fluid compartments in dogs dehydrated by the administration of sucrose or by deprivation of food and water. Extracellular fluid provided a larger proportion of the water lost than did the intracellular fluid when the dehydration was produced by the former method; by the latter method, the intracellular fluid accounted for some 33 to 43 per cent of the water lost. This is a smaller proportion of intracellular fluid lost than previously reported in this condition (186), but these data may be due to the questionable validity of measuring total body water by the apparent volume of distribution of sulphanilamide (187). The fall in plasma volume was proportionately greater than that of extracellular fluid; plasma volume was, therefore, not maintained at the expense of interstitial fluid. Dicker (67) compared the effects of starvation and dehydration in rats. In the starved rats with free access to water the urinary excretion of chloride, sodium, and potassium diminished, and analyses of skeletal muscle showed an expansion of the extracellular (chloride) phase and a decrease in intracellular water and potassium. In the water-deprived rats, the concentrations in serum of chloride, sodium, and potassium increased; the renal excretion of chloride and sodium fell, but that of potassium increased; in skeletal muscle both fluid phases were contracted. The administration of a water load equivalent to five per cent of the body weight, under both experimental conditions, produced a delayed diuresis in starvation and no diuresis in water deprivation. In the latter condition, access to water ad libitum led to overhydration of both fluid phases. Dicker concludes that under these conditions, a renal factor operates to conserve water, as well as the osmotic factors demonstrated by Elkinton & Taffel (186).

Salt depletion through heavy sweating and the resultant

changes in the distribution of body fluids have been investigated experimentally by Ladell (75). Using the balance method for their calculation, changes in the body fluids in normal human subjects depleted in this manner were found to vary according to whether water alone or salt alone was administered. When salt alone, or nothing, was given, the serum chloride concentration became elevated and the intracellular fluid diminished. When water alone was given, the serum chloride concentration fell, the intracellular fluid expanded, and heat cramps developed. The changes in hematocrit value, reflecting changes in plasma volume, were inversely correlated with those of the extracellular fluid volume and directly with the changes in value of intracellular fluid. These experiments add to the evidence that the body acts as an osmometer [*vide supra*, Wolf (29)], that changes in intracellular hydration are of clinical importance, and that salt depletion has deleterious effects on the circulation.

An analysis of the factors in composition and distribution of body fluids, which are responsible for circulatory failure in dehydration and salt depletion, has been attempted experimentally by Elkinton, Winkler & Danowski (63). Diminished plasma and extracellular fluid volumes, intracellular overhydration, and body fluid hypotonicity, were the result of sodium depletion and were associated with marked circulatory failure. Such failure was less severe in pure dehydration when both fluid phases were diminished. Production of hypotonicity with expansion of the extracellular fluid volume, as produced by injecting glucose solutions into nephrectomized dogs, was associated with a rise in cardiac output. Hypotonicity, therefore, appeared less important than reduction of extracellular and plasma volume in the etiology of salt-depletion shock. On the other hand, in such shocked animals neither restoration of tonicity alone by urea diuresis nor of extracellular and plasma volume alone by glucose infusions produced any improvement in the circulation. It appeared, therefore, that both tonicity and volume were important factors in determining the state of the circulation.

*Clinical states of depletion.*—The work just cited has certain clinical implications. Sodium depletion with its associated distortion of the body fluids readily depresses circulatory efficiency. Systemic depletion in the presence of localized excesses (edema)

may be a factor in the maintenance of the latter. As has been pointed out above and emphasized by Peters (188), the beneficial effect of sodium administration may outweigh the danger of further augmentation of the edema. Any therapeutic measure which produces or exacerbates a sodium depletion promotes collapse of the circulation. The subcutaneous injection of salt-free glucose solution is a common therapeutic procedure, yet it has been clearly demonstrated to depress the circulation (189).

Dehydration in excess of electrolyte depletion is also seen in clinical conditions. Rapoport (190) studied 14 children exhibiting hyperosmolarity and hyperelectrolytemia. The basic physiological difficulty was an intake of water which was inadequate in relation to abnormal excretory requirements. The abnormal rates of water expenditure were mainly accounted for by increases in insensible water loss due to fever or to hyperventilation resulting from metabolic acidosis, and to the limited ability of the infant kidney to concentrate solutes and conserve water [*vide supra* (121)].

Extensive data have been obtained on the disturbances of water and electrolytes in infantile diarrhea by Darrow *et al.* (62). By use of the balance method, these investigators have estimated the magnitude of the deficits of water and electrolytes in eight cases and have partitioned the deficits between the extra- and intracellular phases of body fluids. These were calculated on the assumption that at the end of therapy the patients had been fully reconstituted to the normal state. The average deficits per kg. of body weight so calculated were: water, 125 gm., chloride, 9.2 millimols, sodium, 9.5 millimols, and potassium, 10.4 millimols. The intracellular fluid was depleted of potassium and usually contained sodium in excessive amounts. This shift of sodium into cells was thought to account, in the main, for the acidosis; administration of sodium bicarbonate alone merely exaggerated this abnormal relation of intracellular cations. Solutions containing potassium as well as sodium and chloride were found, therefore, to be therapeutically most effective. In making these calculations, corrections were made for losses of chloride, sodium, and potassium through the skin. The concentrations of chloride and sodium in sweat were derived by assuming balances of these ions which would lead to a somewhat greater reconstitution of extracellular as compared to intracellular volume. While this rather circuitous reasoning might

invalidate the precise extent of these corrections for losses in sweat, the over-all magnitude and direction of the exchanges are beyond question.

Similar studies have been made in other clinical conditions with particular emphasis on alterations in intracellular water and cations. Tarail & Elkinton (25) found that depletion of intracellular potassium occurred inevitably in patients receiving no potassium because the kidney does not conserve the ion as it does those of sodium and chloride. Danowski *et al.* (24) measured the uptake of potassium by the cellular phase in patients in diabetic coma. In such patients, Greenman *et al.* (191) and Seldin & Tarail (192) quantitated by the balance technique the transfers of potassium which occur during the first hours of treatment when the serum potassium concentration falls from high to low levels. The evidence indicates that this change in concentration is the result of dilution of the extracellular fluid, continued excretion of potassium, and a decelerated rate of transfer of potassium out of cells. Similar data were obtained during the pre-potassium stage of therapy in infants recovering from vomiting (193).

Other investigations of pathological variations in the distribution of body water can be enumerated. Gordon, McNamara & Benjamin (194) found that premature infants given ammonium chloride appeared clinically dehydrated but gained weight; a shift of water into cells was postulated. Philips *et al.* (195) calculated by the balance technique the changes in fluid distribution in dogs intoxicated with nitrogen mustard. Extracellular fluid was lost as the result of vomiting, diarrhea, and renal salt wasting. Intracellular potassium was lost with increased catabolism and in excess of nitrogen; the latter possibly being due to a unique cytotoxic effect. Eichelberger, Kollros & Walker (68), by the method of tissue analyses, found no significant change in total content or distribution of water and electrolytes in the brain following cerebral concussion. Mudge & Vislocky (65) described the electrolyte and fluid changes in skeletal muscle produced by acidosis and alkalosis. Fox & Baer (196), using tissue analyses and radioactive isotopes, demonstrated the transfer of sodium into, and potassium out of, burned tissues, with a resultant swelling of cells throughout the body.

The experimental data reviewed indicate clearly that our

knowledge of alterations in volume and composition of intracellular fluid is quite fragmentary. That such alterations take place under conditions of physiological and pathological stress is undeniable, but the laws which govern these exchanges of constituents of intracellular fluid have yet to be completely elucidated.

## LITERATURE CITED

1. McQUARRIE, I., *Ann. Rev. Physiol.*, **7**, 127-62 (1945)
2. ADOLPH, E. F., *Ann. Rev. Physiol.*, **9**, 381-408 (1947)
3. ADOLPH, E. F., AND ASSOCIATES, *Physiology of Man in the Desert*, 357 pp. (Interscience Publishers, Inc., New York, 1947)
4. HALD, P. M., *J. Biol. Chem.*, **167**, 499-510 (1947)
5. USSING, H. H., *Physiol. Revs.*, **29**, 127-55 (1949)
6. USSING, H. H., *Nature*, **160**, 262-63 (1947)
7. USSING, H. H., *Acta Physiol. Scand.*, **17**, 1-37 (1949)
8. FRANCK, J., AND MAYER, J. E., *Arch. Biochem.*, **14**, 297-313 (1947)
9. ROSENBERG, T., *Acta Chem. Scand.*, **2**, 14-33 (1948)
10. OSTERHOUT, W. J. V., *J. Gen. Physiol.*, **30**, 439-47 (1947)
11. OSTERHOUT, W. J. V., *J. Gen. Physiol.*, **32**, 553-57 (1949)
12. OSTERHOUT, W. J. V., *J. Gen. Physiol.*, **32**, 559-66 (1949)
13. BOYLE, P. J., AND CONWAY, E. J., *J. Physiol. (London)*, **100**, 1-63 (1941)
14. DEAN, R. B., *Biol. Symposia*, **3**, 331-69 (1941)
15. CONWAY, E. J., *Irish J. Med. Sci.*, 1-44 (Oct.-Nov., 1947)
16. CONWAY, E. J., AND HINGERTY, D., *Biochem. J.*, **42**, 372-75 (1948)
17. LEVI, H., AND USSING, H. H., *Acta Physiol. Scand.*, **16**, 232-49 (1948)
18. MUNTZ, J. A., *J. Biol. Chem.*, **171**, 653-65 (1947)
19. SCHMIDT, G., HECHT, L., AND THANNHAUSER, S. J., *J. Biol. Chem.*, **178**, 733-42 (1949)
20. DIXON, K. C., *Biochem. J.*, **44**, 187-90 (1949)
21. KREBS, H. A., AND EGGLESTON, L. V., *Biochem. J.*, **44**, vii P. (1949)
22. ELKINTON, J. R., WINKLER, A. W., AND DANOWSKI, T. S., *J. Clin. Invest.*, **27**, 74-81, (1948)
23. DARROW, D. C., *J. Pediat.*, **28**, 515-40 (1946)
24. DANOWSKI, T. S., PETERS, J. H., RATHBUN, J. C., QUASHNOCK, J. M., AND GREENMAN, L., *J. Clin. Invest.*, **28**, 1-9 (1949)
25. TARAIL, R., AND ELKINTON, J. R., *J. Clin. Invest.*, **28**, 99-113 (1949)
26. STONE, D., AND SHAPIRO, S., *Am. J. Physiol.*, **155**, 141-46 (1948)
27. SHAPIRO, H., *J. Gen. Physiol.*, **32**, 43-52 (1948)
28. OPIE, E. L., *J. Exptl. Med.*, **89**, 185-208 (1949)
29. WOLF, A. V., *Am. J. Physiol.*, **153**, 499-502 (1948)
30. MOORE, F. D., *Surg. Gynecol. Obstet.*, **86**, 129-47 (1948)
31. SOBERMAN, R. J., BRODIE, B. B., LEVY, B. B., AXELROD, J., HOLLANDER, V., AND STEELE, J. M., *J. Biol. Chem.*, **179**, 31-42 (1949)
32. MESSINGER, W. J., AND STEELE, J. M., *Proc. Soc. Exptl. Biol. Med.*, **70**, 316-18 (1949)

33. SOBERMAN, R. J., *Proc. Soc. Exptl. Biol. Med.*, **71**, 172-73 (1949)
34. ELKINTON, J. R., *J. Clin. Invest.*, **26**, 1088-97 (1947)
35. CLARK, J. K., AND BARKER, H. G., *Proc. Soc. Exptl. Biol. Med.*, **69**, 152-53 (1948)
36. ELKINTON, J. R., *Federation Proc.*, **8**, 41 (1949)
37. HOUCK, C. R., *Federation Proc.*, **8**, 78 (1949)
38. DOMINGUEZ, R., CORCORAN, A. C., AND PAGE, I. H., *J. Lab. Clin. Med.*, **32**, 1192-1202 (1947)
39. BERGER, E. Y., FARBER, S. J., AND EARLE, D. P., JR., *Proc. Soc. Exptl. Biol. Med.*, **66**, 62-66 (1947)
40. ELKINTON, J. R. (Unpublished data)
41. DANOWSKI, T. S., AND GREENMAN, L. (Personal communication, 1948)
42. GAUDINO, M., SCHWARTZ, I. L., AND LEVITT, M. F., *Proc. Soc. Exptl. Biol. Med.*, **68**, 507-11 (1948)
43. GAUDINO, M., AND LEVITT, M. F., *Am. J. Physiol.*, **157**, 387-93 (1949)
44. FELLERS, F. X., BARNETT, H. L., HARE, K., AND McNAMARA, H., *Pediatrics*, **3**, 622-29 (1949)
45. WINKLER, A. W., ELKINTON, J. R., AND EISENMAN, A. J., *Am. J. Physiol.*, **139**, 239-46 (1943)
46. MOORE, F. D., *Science*, **104**, 157-60 (1946)
47. WANG, J.-C., *J. Gen. Physiol.*, **31**, 259-68 (1948)
48. COPE, O., AND MOORE, F. D., *Ann. Surg.*, **126**, 1010-45 (1947)
49. MORSE, M., CASSELS, D. E., AND SCHULTZ, F. W., *Am. J. Physiol.*, **151**, 438-47 (1947)
50. DOXIADIS, S. A., AND GAIRDNER, D., *Clin. Sci.*, **6**, 258-67 (1946-48)
51. WANG, C. F., AND HEGSTED, D. M., *Am. J. Physiol.*, **156**, 218-26 (1949)
52. HOLLANDER, V., CHANG, P., AND CoTUI, F. W., *J. Lab. Clin. Med.*, **34**, 680-87 (1949)
53. HENSCHEL, A., MICHELSEN, O., TAYLOR, H. L., AND KEYS, A., *Am. J. Physiol.*, **150**, 170-80 (1947)
54. KERPTEL-FRONIUS, E., AND KOVACH, S., *Pediatrics*, **2**, 21-23 (1948)
55. GOLLAN, F., *J. Clin. Invest.*, **27**, 352-63 (1948)
56. LING, W. S. M., AND SPRING, H., *Am. J. Med. Sci.*, **215**, 555-67 (1948)
57. OVERMAN, R. R., HILL, T. S., AND WONG, Y. T., *J. Natl. Malaria Soc.*, **8**, 14-31 (1949)
58. FISHMAN, W. H., AND LEVEEN, H. H., *Arch. Surg.*, **55**, 624-31 (1947)
59. FREIS, E. D., AND KENNEY, J. F., *J. Clin. Invest.*, **27**, 283-89 (1948)
60. SUNDERMAN, F. W., AND ROSE, E., *J. Clin. Endocrinol.*, **8**, 209-20 (1948)
61. PAINTER, E. E., HOLMES, J. H., AND GREGERSEN, M. I., *Am. J. Physiol.*, **152**, 66-76 (1948)
62. DARROW, D. C., PRATT, E. L., FLETT, J., JR., GAMBLE, A. H., AND WIESE, H. F., *Pediatrics*, **3**, 129-56 (1949)
63. ELKINTON, J. R., WINKLER, A. W., AND DANOWSKI, T. S., *J. Clin. Invest.*, **26**, 1002-9 (1947)
64. DANOWSKI, T. S., ELKINTON, J. R., BURROWS, B. A., AND WINKLER, A. W., *J. Clin. Invest.*, **27**, 65-73 (1948)

65. MUDGE, G. H., AND VISLOCKY, K., *J. Clin. Invest.*, **28**, 482-86 (1949)
66. DARROW, D. C., SCHWARTZ, R., IANNUCCI, J. F., AND COVILLE, F., *J. Clin. Invest.*, **27**, 198-208 (1948)
67. DICKER, S. E., *Biochem. J.*, **44**, 274-81 (1949)
68. EICHELBERGER, L., KOLLROS, J. J., AND WALKER, A. E., *Am. J. Physiol.*, **156**, 129-36 (1949)
69. MOLE, R. H., *J. Physiol. (London)*, **107**, 399-411 (1948)
70. MARSHALL, L. H., AND SPECHT, H., *Am. J. Physiol.*, **156**, 299-310 (1949)
71. D'ALTON, C. J., DARLING, R. C., AND SHEA, E., *Am. J. Med. Sci.*, **216**, 516-22 (1948)
72. SCHMIDT-NIELSEN, B., *Federation Proc.*, **8**, 139 (1949)
73. PRATT, E. L., COOKE, R. E., AND DARROW, D. C., *Federation Proc.*, **8**, 237-38 (1949)
74. LADELL, W. S. S., *J. Physiol. (London)*, **107**, 465-71 (1948)
75. LADELL, W. S. S., *J. Physiol. (London)*, **108**, 440-50 (1949)
76. CONN, J. W., LOUIS, L. H., JOHNSTON, M. W., AND JOHNSON, B. J., *J. Clin. Invest.*, **27**, 529-30 (1948)
77. CONN, J. W., *Arch. Internal Med.*, **83**, 416-28 (1949)
78. PETERS, J. P., *New Engl. J. Med.*, **239**, 353-62 (1948)
79. PETERS, J. P., *McGill Med. J.*, **28**, 130-45 (1949)
80. PITTS, R. F., *The Interne*, April-May, 94-131 (1949)
81. VERNEY, E. B., *Proc. Roy. Soc. (London)* [B]**135**, 25-106 (1947)
82. HALL, C. A., FRAME, B., AND DRILL, V. A., *Endocrinology*, **44**, 76-82 (1949)
83. LESLIE, S. H., AND RALLI, E. P., *Endocrinology*, **41**, 1-11 (1947)
84. WATSON, C. J., AND GREENBERG, A., *Am. J. Med. Sci.*, **217**, 651-57 (1949)
85. ELLIS, M. E., AND GROLLMAN, A., *Endocrinology*, **44**, 415-19 (1949)
86. WILKINS, R. W., CULBERTSON, J. W., BURROWS, B. A., TINSLEY, C. M., JUDSON, W. E., AND BURNETT, C. H., *J. Clin. Invest.*, **28**, 819 (1949)
87. BADER, R. A., ELIOT, J. W., AND BASS, D. E., *Federation Proc.*, **8**, 7 (1949)
88. STRAUSS, M. B., ROSENBAUM, J. D., AND NELSON, W. P., 3d, *J. Clin. Invest.*, **28**, 813-14 (1949)
89. WALKER, J. M., *Quart. J. Med.*, **18**, 51-55 (1949)
90. FERRER, M. I., AND SOKOLOFF, L., *Am. J. Med. Sci.*, **214**, 372-84 (1947)
91. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G., AND HILLS, A. G., *J. Clin. Endocrinol.*, **8**, 15-66 (1948)
92. PRUNTY, F. T. G., FORSHAM, P. H., AND THORN, G. W., *Clin. Sci.*, **7**, 109-20 (1948)
93. ELKINTON, J. R., HUNT, A. D., JR., GODFREY, L., MCCRORY, W. W., ROGERSON, A. G., AND STOKES, J. J., *J. Am. Med. Assoc.* (In Press)
94. MCALPINE, H. T., VENNING, E. H., JOHNSON, L., SCHENKER, V., HOFFMAN, M. M., AND BROWNE, J. S. L., *J. Clin. Endocrinol.*, **8**, 591 (1948)
95. SAYERS, G., BURNS, T. W., TYLER, F. H., JAGER, B. V., SCHWARTZ, T. B., SMITH, E. L., SAMUELS, L. T., AND DAVENPORT, H. W., *J. Clin. Endocrinol.*, **9**, 593-614 (1949)
96. MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIARAMELLI, L. C., LI, C. H., AND EVANS, H. M., *J. Clin. Endocrin.*, **8**, 1-14 (1948)

97. INGLE, D. J., LI, C. H., AND EVANS, H. M., *Endocrinology*, **39**, 32-42 (1946)
98. FORSHAM, P. H., FLINK, E., EMERSON, K., JR., AND THORN, G. W., *J. Clin. Invest.*, **28**, 781 (1949)
99. OSBORN, C. M., AND EVERSOLE, W. J., *Federation Proc.*, **8**, 122 (1949)
100. LOTSPEICH, W. D., *Endocrinology*, **44**, 314-16 (1949)
101. BIRNIE, J. H., EVERSOLE, W. J., BOSS, W. R., OSBORN, C. M., AND GAUNT, R., *Federation Proc.*, **8**, 12 (1949)
102. SARTORIUS, O. W., AND ROBERTS, K., *Federation Proc.*, **8**, 138-39 (1949)
103. SKAHEN, J. G., AND GREEN, D. M., *Am. J. Physiol.*, **155**, 290-94 (1948)
104. LITTLE, J. M., WALLACE, S. L., WHATLEY, E. C., AND ANDERSON, G. A., *Am. J. Physiol.*, **151**, 174-85 (1947)
105. ANSLOW, W. P., JR., WESSON, L. G., JR., BOLOMEY, A. A., AND TAYLOR, J. G., *Federation Proc.*, **7**, 3 (1948)
106. SMITH, H. W., *Bull. N. Y. Acad. Med.*, **23**, 177-95 (1947)
107. WESSON, L. G., ANSLOW, W. P., JR., AND SMITH, H. W., *Federation Proc.*, **7**, 132 (1948)
108. WESSON, L. G., JR., AND ANSLOW, W. P., JR., *Am. J. Physiol.*, **153**, 465-74 (1948)
109. CIZEK, L. J., AND HOLMES, J. H., *Federation Proc.*, **7**, 21 (1948)
110. RAPOPORT, S., BRODSKY, W. A., WEST, C. D., AND MACKLER, B., *Science*, **108**, 630-32 (1948)
111. RELMAN, A. S., GOODYER, A. V. N., AND PETERSON, E. R., *J. Applied Physiol.*, **1**, 601 (1949)
112. CRUTCHFIELD, A. J., JR., AND WOOD, J. E., *Ann. Internal Med.*, **28**, 28-40 (1948)
113. RAPOPORT, S., WEST, C. D., AND BRODSKY, W. A., *Am. J. Physiol.*, **157**, 363-86 (1949)
114. SELDIN, D. W., AND TARAIL, R., *Am. J. Physiol.*, **159**, 160-74 (1949)
115. RAPOPORT, S., BRODSKY, W. A., WEST, C. D., AND MACKLER, B., *Am. J. Physiol.*, **156**, 433-42 (1949)
116. RAPOPORT, S., BRODSKY, W. A., AND WEST, C. D., *Am. J. Physiol.*, **157**, 357-62 (1949)
117. PRATT, E. L., BIENVENU, B., AND WHYTE, M. M., *Pediatrics*, **1**, 181-87 (1948)
118. SMITH, C. A., YUDKIN, S., YOUNG, W., MINKOWSKI, A., AND CUSHMAN, M., *Pediatrics*, **3**, 34-48 (1949)
119. McCANCE, R. A., AND WILKINSON, E., *J. Physiol. (London)*, **106**, 256-63 (1947)
120. HELLER, H., *J. Physiol. (London)*, **106**, 245-55 (1947)
121. McCANCE, R. A., *Physiol. Revs.*, **28**, 331-48 (1948)
122. ADOLPH, E. F., *Am. J. Physiol.*, **155**, 309-16 (1948)
123. ADOLPH, E. F., AND PARMINGTON, S. L., *Am. J. Physiol.*, **155**, 317-26 (1948)
124. ARCHDEACON, J. W., PRESNELL, M. W., AND WALTON, C. J., *Am. J. Physiol.*, **157**, 149-52 (1949)
125. STARR, I., *Ann. Internal Med.*, **30**, 1-23 (1949)

126. WESSON, L. G., JR., ANSLOW, W. P., JR., AND SMITH, H. W., *Bull. N. Y. Acad. Med.*, **24**, 586-606 (1948)
127. LEITER, L., *Bull. N. Y. Acad. Med.*, **24**, 702-19 (1948)
128. PAINE, R., AND SMITH, J. R., *Am. J. Med.*, **6**, 84-102 (1949)
129. STEAD, E. A., JR., *Am. J. Med.*, **6**, 232-36 (1949)
130. MERRILL, A. J., *Am. J. Med.*, **6**, 357-67 (1949)
131. BRADLEY, S. E., AND BLAKE, W. D., *Am. J. Med.*, **6**, 470-80 (1949)
132. MCMICHAEL, J., *Am. J. Med.*, **6**, 651-61 (1949)
133. DAVIS, J. O., AND SMITH, J. R., *Am. J. Med.*, **3**, 704-17 (1947)
134. RICHARDS, D. W., JR., *Am. J. Med.*, **6**, 772-80 (1949)
135. BURCH, G., REASER, P., AND CRONVICH, J., *J. Lab. Clin. Med.*, **32**, 1169-91 (1947)
136. THREEFOOT, S., BURCH, G., AND REASER, P., *J. Lab. Clin. Med.*, **34**, 1-13 (1949)
137. GORHAM, L. W., LEITER, D. E., WOLF, A. V., AND SHULTZ, H. H., *Ann. Internal Med.*, **27**, 575-83 (1947)
138. WARREN, J. V., AND STEAD, E. A., JR., *Arch. Internal Med.*, **73**, 138 (1944)
139. MERRILL, A. J., *J. Clin. Invest.*, **25**, 389-400 (1946)
140. MOKOTOFF, R., ROSS, G., AND LEITER, L., *J. Clin. Invest.*, **27**, 1-9 (1948)
141. BORST, J. G. G., *Acta Med. Scand.*, **130**, Suppl. No. 207, 1-71 (1948)
142. BRIGGS, A. P., FOWELL, D. M., HAMILTON, W. F., REMINGTON, J. W., WHEELER, N. C., AND WINSLOW, J. A., *J. Clin. Invest.*, **27**, 810-17 (1948)
143. EARLE, D. P., JR., FARBER, S. J., ALEXANDER, J. D., AND EICHNA, L. W., *J. Clin. Invest.*, **28**, 778 (1949)
144. KALTUS, A., GENECIN, A., SISSON, J. H., MONGE, C., SINCLAIR-SMITH, B. C., AND NEWMAN, E. V., *J. Clin. Invest.*, **28**, 793 (1949)
145. NEWMAN, E. V., *Am. J. Med.*, **7**, 490-96 (1949)
146. ELKINTON, J. R., SQUIRES, R. D., CROSLEY, A. P., JR., AND CLARK, J. K. (Unpublished data)
147. GREEN, D. M., FARAH, A., JOHNSON, A. D., AND BRIDGES, W. C., *Proc. 22d Scientific Sessions, Am. Heart Assoc.*, 27-28 (Atlantic City, N. J., June 3-4, 1949)
148. GALDSTON, M., BERGER, E. Y., AND HORWITZ, A. S., *J. Clin. Invest.*, **28**, 783 (1949)
149. BERGER, E. Y., GALDSTON, M., AND HORWITZ, S. A., *J. Clin. Invest.*, **28**, 648-52 (1949)
150. BRADLEY, S. E., MUDGE, G. H., BLAKE, W. D., AND ALPHONSE, P., *J. Clin. Invest.*, **28**, 772 (1949)
151. BLAKE, W. D., WEGRIA, R., KEATING, R. P., AND WARD, H. P., *Am. J. Physiol.*, **157**, 1-13 (1949)
152. MAXWELL, M. H., BREED, E. S., AND SCHWARTZ, I. L., *Federation Proc.*, **8**, 108 (1949)
153. SELKURT, E. E., HALL, P. W., AND SPENCER, M. P., *Am. J. Physiol.*, **157**, 40-46 (1949)
154. PARRISH, A. E., *J. Clin. Invest.*, **28**, 45-49 (1949)
155. MERRILL, A. J., *Proc. 22d Scientific Session, Am. Heart Assoc.*, 39 (1949)

156. BERCU, B. H., ROKAW, S. N., AND MASSIE, E., *Proc. 22d Scientific Session, Am. Heart Assoc.*, 21 (1949)
157. MOKOTOFF, R., ESCHER, D. J. W., EDELMAN, I. S., GROSSMAN, J., LEITER, L., WESTON, R. E., ZWEIFACH, B. W., AND SHORR, E., *Federation Proc.*, 8, 112 (1949)
158. WELT, L. G., AND ORLOFF, J., *J. Clin. Invest.*, 28, 818 (1949)
159. ORLOFF, J., WELT, L. G., AND STOWE, L., *J. Clin. Invest.*, 28, 802 (1949)
160. SCHEMM, F. R., *Ann. Internal Med.*, 30, 92-99 (1949)
161. FOX, C. L., JR., FRIEDBURG, C. K., AND WHITE, A. G., *J. Clin. Invest.*, 28, 781-82 (1949)
162. FARNSWORTH, E. B., *Am. J. Med.*, 4, 338-42 (1948)
163. FARNSWORTH, E. B., AND KRAKUSIN, J. S., *J. Lab. Clin. Med.*, 33, 1534-44 (1948)
164. SCHROEDER, H. A., *J. Clin. Invest.*, 28, 809 (1949)
165. SCHROEDER, H. A., *J. Am. Med. Assoc.*, 141, 117-24 (1949)
166. MACGUIRE, W. B., JR., *J. Am. Med. Assoc.*, 137, 1377-78 (1948)
167. SOLOFF, L. A., AND ZATUCHNI, J., *J. Am. Med. Assoc.*, 139, 1136-39 (1949)
168. KLINGHOFFER, K. A., *New Intern. Clinics*, [4]1, 221-26 (1941)
169. MANKIN, H., AND LOWELL, A., *J. Clin. Invest.*, 27, 145-53 (1948)
170. KUNKEL, H. G., EISENMENGER, W. J., AND AHRENS, E. H., JR., *J. Clin. Invest.*, 28, 794-95 (1949)
171. MCKEE, F. W., SCHLOERB, P. R., SCHILLING, J. A., TISHKOFF, G. H., AND WHIPPLE, G. H., *J. Exptl. Med.*, 87, 457-71 (1948)
172. FARNSWORTH, E. B., AND KRAKUSIN, J. S., *J. Lab. Clin. Med.*, 33, 1545-54 (1948)
173. FOX, C. L., JR., AND McCUNE, D. J., *Am. J. Med. Sci.*, 216, 1-10 (1948)
174. LEUTSCHER, J. A., JR., AND HALL, A. D., *J. Clin. Invest.*, 27, 548 (1948)
175. EDER, H. A., CHINARD, F. P., LAUSON, H. D., GREIF, R. L., HILLER, A., COTZIAS, G. C., AND VAN SLYKE, D. D., *J. Clin. Invest.*, 28, 779 (1949)
176. BURNETT, C. H., BURROWS, B. A., AND COMMONS, R. R., *J. Clin. Invest.*, 28, 773 (1949)
177. TOBIAN, L., *J. Clin. Endocrinol.*, 9, 319-29 (1949)
178. MARRIOTT, H. L., *Brit. Med. J.*, 1, 245-50, 285-90, 328-32 (1947)
179. DARROW, D. C., *Bull. N. Y. Acad. Med.*, 24, 147 (1948)
180. ADOLPH, E. F., *Am. J. Physiol.*, 151, 564-75 (1947)
181. SCHMIDT-NIELSEN, K., *Federation Proc.*, 8, 140 (1949)
182. SCHMIDT-NIELSEN, K., SCHMIDT-NIELSEN, B., AND SCHNEIDERMAN, H., *Am. J. Physiol.*, 154, 163-66 (1948)
183. SPEALMAN, C. R., YAMAMATO, W., BIXBY, E. W., AND NEWTON, M., *Am. J. Physiol.*, 152, 233-41 (1948)
184. SIEGEL, P. S., ALEXANDER, I. E., AND STUCKEY, H. L., *Am. J. Physiol.*, 150, 729-32 (1947)
185. HELLER, H., *J. Physiol. (London)*, 108, 303-14 (1949)
186. ELKINTON, J. R., AND TAFFEL, M., *J. Clin. Invest.*, 21, 787 (1942)
187. ELKINTON, J. R., AND TAFFEL, M., *Am. J. Physiol.*, 138, 126 (1942)
188. PETERS, J. P., *Surgery*, 24, 568-70 (1948)

189. DANOWSKI, T. S., WINKLER, A. W., AND ELKINTON, J. R., *J. Clin. Invest.*, **26**, 887-91 (1947)
190. RAPOPORT, S., *Am. J. Diseases Children*, **74**, 682-702 (1947)
191. GREENMAN, L., MATEER, F. M., GOW, R., PETERS, J. H., AND DANOWSKI, T. S., *J. Clin. Invest.*, **28**, 409-13, (1949)
192. SELDIN, D. W., AND TARAIL, R., *J. Clin. Invest.*, **28**, 810 (1949)
193. DANOWSKI, T. S., GREENMAN, L., PETERS, J. H., GOW, R., AND MATEER, F., *J. Clin. Invest.*, **28**, 777 (1949)
194. GORDON, H. H., McNAMARA, H., AND BENJAMIN, H. R., *Pediatrics*, **2**, 290-302 (1948)
195. PHILIPS, F. S., GILMAN, A., KOELLE, E. S., McNAMARA, B. P., AND ALLEN, R. P., *Am. J. Physiol.*, **155**, 295-308 (1948)
196. FOX, C. L., JR., AND BAER, H., *Am. J. Physiol.*, **151**, 155-67 (1947)
197. FERRARO, L. R., FRIEDMAN, M. M., AND MORELLI, H. E., *Arch. Internal Med.*, **83**, 292-97 (1949)
198. DICKER, S. E., *Biochem. J.*, **43**, 444-53 (1948)
199. DICKER, S. E., *Biochem. J.*, **43**, 453-61 (1948)

## RESPIRATORY SYSTEM<sup>1</sup>

BY WALLACE O. FENN, HERMANN RAHN, AND ARTHUR B. OTIS

*The Department of Physiology and Vital Economics, The University of  
Rochester School of Medicine and Dentistry, Rochester, New York*

*Monographs and reviews.*—Monographs and reviews of interest to respiratory physiologists include a new edition of Barach's book (12) dealing with physiologic therapy of respiratory diseases, a well annotated bibliography on submarine medicine edited by Hoff (93), Monge's discussion of historical and philosophical aspects of acclimatization in the Andes (124), Grandjean's reviews of adaptation to mountainous environments (79, 80), a review by van Goor (190) covering the distribution and physiological significance as well as the chemical properties of carbonic anhydrase, a translation of a symposium on German submarine medicine (167), and certain chapters in the *Fiat Review of German Science* (150), which covers literature that has been largely unavailable to workers in this country. Finally a series of papers concerning problems of respiration and high altitudes have been published by Verzar in monograph form from the Basel Institute of Physiology (192).

### LUNG VOLUMES AND RESPIRATORY MECHANICS

Baarsma & Dirken (8) experimentally demonstrated the presence of collateral communications between parts of a pulmonary lobe in the rabbit. Since the resistance to air flow of these communications is independent of pressure, they appear to be permanent structures; and histological study showed the presence of stomata bordered by capillaries. Such connections do not exist between lobes of the lung except in a few cases where a tissue bridge was found. Evidence of similar intralobular connections in man was presented by Baarsma, Dirken & Huizinga (9), who conclude that atelectasis can not occur from the presence of a foreign object unless a whole lobe is blocked. The clinical importance of collateral ventilation is also discussed by Churchill (37).

Lawton & King (109) have made a mathematical analysis of the elastic properties of rat lungs, assuming each alveolus to be a hollow shell composed of rubber-like molecules and the whole lung to be a multiple of such a unit. Some experiments by Arshavski (4) indicate that in the cat fetus (nearly full term), about 10

<sup>1</sup> This review covers the period from April, 1948 to June, 1949.

cm. water negative intrapleural pressure must be developed before the lungs will expand. The old question of the greatest depth in water at which one can breathe through a tube to the surface was reinvestigated by Mackay (115), who finds the maximum to be about five feet.

Interest continues in the measurement of lung volume, especially residual air. Meneely & Kaltreider (122) describe a closed circuit helium method that requires about 7 min. for completion. Willmon & Behnke (200) find that residual volumes measured by a volume expansion method (in which the subject is rapidly decompressed from four atmospheres to one) are similar in magnitude but more variable than those measured by helium or nitrogen dilution methods. An excellent paper by Gilson & Hugh-Jones (78) shows that a helium dilution method agrees with a nitrogen elimination method up to functional residual volumes of 4.5 l., above which the helium method gives larger values. The helium method is considered to be more nearly correct for the larger volumes, because the recognized errors would not make it give too large values, whereas errors inherent in the nitrogen method would tend to make the results too small. The same authors argue that the mean of at least three repeat measurements of vital capacity is a better estimate than the maximum reading if the range is less than 200 cc. Rahn, Fenn & Otis (145) discuss reasons for a modification of the Lundsgaard-VanSlyke method for residual air and present data showing that the average standard deviation of daily determinations on five subjects over a two-month period was 5.5 per cent of the residual volume. Almost exactly the same variation was recorded by Chiodi (35) using a modified Christie technique on tuberculosis patients. The lung volumes of emphysematous patients were found by Motley, Lang & Gordon (127) to be unaffected by daily treatments with intermittent positive pressure breathing.

Gilson & Hugh-Jones (78) show that maximal voluntary breathing capacity (MBC) is more closely correlated with the complemental air volume than with vital capacity, and Motley, Lang & Gordon (128) claim that degree of emphysema (defined

as the ratio,  $\frac{\text{Residual air}}{\text{Vital Capacity} + \text{Residual air}}$ ) is better correlated with

MBC than with vital capacity. Otis & Bembower (133) find that

MBC shows a negative correlation with resistance of the airways as well as a positive correlation with vital capacity, and that the highest score in the test is obtained when the tidal volumes are at least 0.3 of the vital capacity.

Stephen (180) measured vital capacity in various positions commonly used during surgical operations and observed that the prone position gives the smallest values and the reverse Trendelenburg (35°) the largest. Lo Monaco-Croce *et al.* (111) noted that both the alveolar and total ventilations are lower in the supine position than in several other positions tested. The effects of positive and negative acceleration with and without protective devices on the lung volumes and on the depth and frequency of breathing were measured on human subjects by Lombard *et al.* (110).

*Nervous regulation of respiration.*—Respiratory inhibitions have been induced by stimulation of various regions of the cortex of monkeys [Kaada *et al.* (99)]. Hoff & Breckenridge (94) feel that the medullary respiratory center in the dog can maintain periodic respiration in the absence of the pons and the vagus nerve. Borison (25) describes a specific area in the myelencephalon responsible for spasmodic respiratory events such as sneezing, coughing, and retching. Larrabee & Hodes (108) have given us a detailed analysis of the cyclic changes in the respiratory center as revealed by the effects of variously timed afferent impulses sent in over the superior laryngeal nerve, on the electrical activity of the phrenic nerve. The threshold number of afferent impulses required to stop inspiration decreased linearly with the progression of the inspiratory phase. Afferent volleys during expiration delay the start of the next inspiration. These and many other observations are best interpreted on the assumption of cyclic changes somewhere in the respiratory center which monitor the normally occurring afferent impulses. Rijlant (152) demonstrated fibre groups which transmit the phasic control to the phrenics while others are identified with modulation of this cycle.

Various afferents arising in the lungs which modify the central activity have been investigated by numerous techniques. Scott *et al.* (172) have studied the rate of recovery of the Hering-Breuer reflex after respiratory arrest induced by barbiturates. Bakos & Howell (10) suggest the application of midthoracic constriction to maintain adequate respiration during such narcosis. The effect of posture on the respiration rate of dogs has been demonstrated by

Reed & Scott (149). These changes are interpreted on the basis of lung volume changes initiating the excitatory or inhibitory Hering-Breuer reflexes. Aviado & Pontius (7) have shown that the apnea following veratridine is initiated by pulmonary receptors. The importance of afferents in the crossed phrenic phenomenon has been reinvestigated by Chatfield & Mead (33). The role of limb reflexes during exercise upon the ventilation have been studied by Asmussen & Nielsen (5). They feel that such proprioceptors are responsible for the initial ventilation at the onset of exercise, while Gardner & Jacobs (76) believe that they play an insignificant role during exercise. Otis (131, 132) has calculated the ventilation stimulus arising from the limbs per se during passive exercise by the application of Gray's theory. Such movements account for a ventilation increment of 100 to 150 per cent of resting ventilation. Part of the increment of passive exercise ventilation is due to an increased oxygen consumption (132, 166). Morgan & Grodins (82, 125) compared the ventilation and acid-base shifts in dogs with and without spinal section (T-10) before and during exercise. Spinal animals exhibited respiratory and metabolic acidosis during exercise.

*Chemical regulation of respiration.*—Hesser (91) has investigated the role of the centrogenic and the chemoreflex components of respiration during changes in the acid-base balance. These studies support the concept that the concentration of hydrogen ions within the center is the dominating factor controlling respiratory activity and that the concentration of hydrogen ions lags only slightly behind the arterial changes. Chemoreflex drive is more important during eupnea and alkalosis than under metabolic acidosis. The effects of oxygen tension upon the ventilation has been investigated under various sorts of circumstances. The threshold value of inspired oxygen during progressive anoxia and exercise which induces hyperventilation was found to be quite variable [Georg & Sonne (77)]. Dogs with denervated chemoreceptors exhibited various patterns from inspiratory inhibition to stimulation when subjected to low oxygen pressures for short periods [Cordier & Cordier (39)]. The greater stimulatory effect of high carbon dioxide concentration with oxygen instead of air [Cordier & Cordier (40)] as well as the temporary apnea produced by pure oxygen after anoxia [Grandpierre *et al.* (81)] is attributed to a direct effect of oxygen upon the respiratory center. Chiodi *et al.*

(36) report an increased ventilation with pure oxygen in normal subjects, as well as in anemia patients, thus showing that the latter were normally under no hypoxic stimulation. Weterlings (195) proposes a theory that the arterial  $pO_2$  has an inhibitory effect, while carbon dioxide has an excitatory effect upon the ventilation. Any change may thus be explained on the balance between these two factors acting through the chemoreceptors.

Altered chemical states of the body and their effects upon ventilation are described by various authors. Heerhaber (88) has shown that the alveolar carbon dioxide is lowered and a slight increased sensitivity to carbon dioxide is found during the post-ovulatory period of the menstrual cycle. Santenise *et al.* (160) have found similar sensitivity changes related to the glycemia level in the blood, while Berg (14) has shown that carbon dioxide elimination during recovery from exercise is more rapid if the alkali reserve has been raised. Ament *et al.* (2) have measured continuously the changes in alveolar air and ventilation throughout the various stages of pentothal anesthesia.

*Alveolar gas exchange.*—Riley & Cournand (153) and Rahn (143, 144) have been able to define theoretically the "ideal" or mean alveolar air composition, knowing the mixed venous blood composition, the inspired gas tension, and the respiratory quotient, and to calculate the exact ventilation-perfusion ratios which are responsible for any particular alveolar composition. The so-called "venous admixture" to the pulmonary circulation has been determined by Lambertson *et al.* (106) from the arterial-alveolar oxygen gradient breathing pure oxygen and by Douglas *et al.* (53) from the inspired oxygen tension at which complete hemoglobin saturation is obtained. The unequal mixing of gases in the lung has been studied by Fowler (72) by washing out the lungs with a single breath of oxygen and determining the changes in nitrogen concentration during the ensuing expiration by means of an instantaneous nitrogen analyzer. He finds that the inspired oxygen is not evenly distributed throughout the functional residual air and that poorly ventilated areas empty later. Boothby *et al.* (23) find that it takes about 3 min. to wash out the lungs with pure oxygen.

The various factors which may alter the physiological dead space have been determined by Fowler (73) using the fast nitrogen analyzer. Stannard & Russ (178) have compared the effects of added dead space upon the ventilation and alveolar carbon dioxide

at rest and during exercise, while Gladston & Horwitz (75) have measured the gas exchange in the supraglottic region of the respiratory dead space contributed by the mucous membranes.

*Pulmonary circulation.*—Drinker (55) has given us an informative review concerning our present knowledge of the nervous regulation of respiratory phenomena and pulmonary flow, while Trueta (187) has presented a historical account of Servetus, the first to describe the lesser circulation in 1546. Rodbard & Brown (155) have made a comparative study among the various vertebrates, surveying the differences between pulmonary and systemic arterial pressures. Ligation of one pulmonary artery increases the pulmonary arterial pressure [Euler & Liljestrand (62)] and the right ventricular pressure [Long *et al.* (112)]. Cournand *et al.* (44) found similar changes in man after lung resection but only during exercise. Dirken & Heemstra (49, 50, 51), by means of a tracheal divider, exposed one lung to various oxygen tensions or to aerosols containing drugs. The consequent changes in pulmonary flow could then be estimated from the changes in oxygen content or oxygen tension of the mixed arterial blood. Nitrogen administration to one lung will reduce the pulmonary flow in that lung eventually to less than half. Epinephrine and histamine induce vasoconstriction. Administration of 20 to 30 per cent carbon dioxide in monkeys [Hebb & Nimmo-Smith (87)] and 10 per cent carbon dioxide in dogs [Duke (56, 57) raises the pulmonary arterial pressure while Meeter (120) observed reduction in cardiac output and increase in heart size. Von Euler & Liljestrand (62) present evidence that oxygen acts directly on the pulmonary vessels to induce a pressure rise under low tensions and a pressure fall under high tensions of oxygen. Daly *et al.* (45) and Binet & Burnstein (15) have shown that stimulation of the sympathetic chain will raise the pulmonary arterial pressure and reduce the flow as much as 30 per cent (45). Vagotomy has no effect (51, 15). Acute bradycardia induced by vagal stimulation and acetylcholine increases the pulmonary venous pressure [Campbell *et al.* (32)]. Borden *et al.* (24) have presented evidence that the raised pulmonary arterial pressure in chronic emphysema is due to the increased resistance of the vascular bed.

The pulmonary capillary pressure has been estimated to be 8 to 9 mm. Hg on the basis of pressure recordings from catheters occluding pulmonary arterial and venous branches [Hellemes *et al.* (89) and Dexter *et al.* (46)]. Rakshit (148) and Verloop (191) have

demonstrated communicating vessels between the bronchial and pulmonary artery in the guinea pig, rat, rabbit, and mouse. Roh *et al.* (156) have demonstrated in man a slight gas exchange in one lung after ligation of the pulmonary artery. This is attributed to the bronchial circulation. Swan & Mulligan (183) report that the engorgement following ligation of the upper lobe pulmonary vein eventually resolves itself and normal function is reestablished.

*Effects of exposure to high and low carbon dioxide concentrations.*—As first observed by Bert, if air is the gas originally present in a closed space, the observable symptoms of an animal or person confined therein will be due primarily to the increasing carbon dioxide concentration, although the ultimate death will be caused by low oxygen [Fenn (65), Schaefer (167)]. Numerous observations have been made aboard submarines on actual cruises during which carbon dioxide was present up to 3 per cent and oxygen was lowered an equivalent amount. In one "snorkel" operation a crew spent four weeks without actually surfacing, and the carbon dioxide was 5 to 5.5 per cent. Symptoms included a rise in skin temperature, a drop in rectal temperature, rapid breathing at first, followed by recovery of normal breathing, fall in systolic blood pressure, increased decholine circulation time, decreased pulse rate, approach to circulatory collapse, and a psychological breakdown. Schaefer refers to these symptoms in general as a "vagotonic state" and attributes them largely to the carbon dioxide. Surfacing after long carbon dioxide exposures frequently gave flickering scotomata and headaches. Hayter & Duffner (86) observed in chamber experiments that such headaches disappeared more quickly if oxygen instead of air is breathed following the exposure to carbon dioxide.

Schaefer (167) found that men living for eight days in a chamber containing 3 per cent carbon dioxide showed after two days a decreased sensitivity to this gas as indicated by a diminution of the initial hyperpnea, and by a lessened ventilatory response to higher carbon dioxide concentrations. The carbon dioxide dissociation curve of the blood rose during the exposure. Prolonged reduction of the carbon dioxide tension of the body produces opposite effects as demonstrated by Brown *et al.* (27), who hyperventilated men for 24 hr. in a Drinker respirator. Plasma carbon dioxide diminished and the ventilatory response to carbon dioxide was increased. During one-hour periods of hyperventilation with the

aid of a pneumolator, Fenn *et al.* (67) noted a fall in the alveolar carbon dioxide tension to 20 mm., a rise in the blood lactic acid accompanied by an equivalent fall in the alkaline reserve and an increase in base excretion in the urine. As acapnia developed, the chest seemed to expand less for the same applied intrapulmonary pressure. Hyperventilation was found by Campbell *et al.* (31) to produce a decrease in the plasma inorganic phosphate of curarized but not anesthetized dogs.

Exposure of rabbits or cats to 1.8 to 7 per cent carbon dioxide for 6 hr. produces an increase in the potassium/calcium ratio of the plasma and an increase in the alkaline reserve, but exposure to higher carbon dioxide concentrations causes less change in the potassium/calcium ratio and a decrease in the alkaline reserve [Schaefer (167), Malorny (117)]. These changes involve complex shifts of ions and water between the blood and tissues and deserve further study by experiments continued, if possible, until a new steady state is reached.

Colldahl (38) found that tissues sampled from guinea pigs that had been exposed to 25 to 30 per cent carbon dioxide showed a lowered oxygen consumption and believes that this is a specific effect of the carbon dioxide because ammonium chloride acidosis did not show a similar action. Another general response of the body to high carbon dioxide is indicated by the experiments of Fortier (69), who found that exposure of rats to 15 per cent carbon dioxide plus 19 per cent oxygen for 38 hr. is a stimulus to the "alarm reaction" as judged by adrenal hyperplasia and splenic and thymic involution.

*Low oxygen and high altitudes.*—The highest altitude tolerated by men breathing oxygen without loss of consciousness was set by Dill & Penrod (47, 48) at 44,800 feet. The ventilation varied greatly in the eight men studied, the lowest alveolar carbon dioxide tension being 12 mm. All of these subjects were close to collapse. Some diminution in performance has been shown at altitudes as low as 10,000 feet breathing air [Fiset & Dugal (68)]. With a warning device built to signal the presence of slow 5 to 7 per sec. waves in the electrical discharge of the brain it was shown in a study of 107 subjects that this warning is given 60 sec. in advance of interference with the ability to write or the onset of other mental disturbances [Prast & Noell (140)]. The duration of useful consciousness breathing oxygen at altitudes from 30,000 to 42,000 feet has

been carefully measured by Hall (85). In a series of subjects giving and receiving transfusion to lower or raise respectively the number of red cells in the blood it was found that the duration of useful consciousness was varied inversely with the number of red cells. In rabbits it has been found, however, that an increase in red count amounting to 84 per cent in excess of the normal may be disadvantageous. This level was reached by repeated transfusions coupled with daily exposures to high altitudes. Such animals became unhealthy, lost weight, and died in 26 to 177 days [Bancroft (11)]. Altland (1) found that a short exposure to altitude every two to three days is sufficient to maintain a polycythemia due to previous altitude acclimatization. One sign of acclimatization in rats by previous daily exposures to altitude is a more rapid increase in ventilation during a simulated ascent as compared to normal unacclimatized controls [Reynolds (151)].

The increase in the red count must be regarded as merely an inexpensive substitute for an increase in the cardiac output. Hurtado & Aste-Salazar (96) have shown that even after 14 weeks of acclimatization the count does not equal that of the natives in the high altitudes of Peru. Samples of the bone marrow were aspirated from the sternum through a needle in 16 such Peruvian natives and were found to show hyperplasia and increased cellularity in 81 per cent. The increase was in the erythroid, not the myeloid cells. This result was interpreted as indicating that hypoxia acts as a specific stimulus to the bone marrow [Merino *et al.* (123)]. A somewhat different theory of the adequate stimulus was expressed by Bonsdorff (22). Northup & Bell (130) have reported that daily sublethal injections of potassium cyanide will act like altitude anoxia in stimulating the bone marrow to cause polycythemia.

The greater resistance of infant animals to anoxia is well-known, but Cheymol (34) has shown that in the guinea pig which is born fully developed this difference is much less marked. He finds that the resistance to anoxia diminishes with age in two distinct steps. The second step occurs at the age of two months in the cat and is correlated with changes in tissue respiration and composition which assume adult characteristics at that age. Strictly speaking the infant mortality in the high altitude regions of Bolivia is an unrelated problem but this has been reported to be high on a statistical basis compared to lower altitudes. There

is no proof, however, that the observed difference is really related to the low oxygen per se. (59).

A review of drugs and diets useful at altitude [Smith (174)] reports no really useful discoveries except for those slight advantages from procedures which lower the metabolic rate, or stimulate respiration, or raise the R.Q. (glucose). An aqueous extract of the adrenal cortex prepared by Kendall was found effective in improving the altitude tolerance of mice by Kottke *et al.* (103) but two commercial extracts and Doca were both ineffective. Increasing or decreasing the size of the adrenals by experimental means had no effect on the altitude tolerance. In the adrenal of rats it has been found that the gland gains water and loses lipids particularly in the zona fasciculata and reticularis, these effects being mediated probably through the corticotrophic hormone of the pituitary [Nichols (129)].

Some improvement in altitude tolerance has been claimed by the use of compounds which are related to the oxidative systems of the tissues. These include nicotinic acid and nicotinamide [Calder (30)]. Brooks (26) has shown that a dose of methylene blue by mouth both prevents and cures symptoms of altitude sickness on short trips from sea level into the high mountains in Peru. The alleged usefulness of cytochrome-*c* for this purpose has not been confirmed [Mellinger (121), Eckenhoff *et al.* (58), and Rabinovitch *et al.* (142)]. It is difficult to see how any such substance could be of any real use in the tissues unless it served to saturate the enzymes with oxygen at an unusually low partial pressure, and from the evidence available this seems unlikely.

*Composition of alveolar air at altitude.*—Changes in the composition of the alveolar air at altitude have been recorded by a continuous sampling and recording apparatus. When plotted on carbon dioxide tension versus oxygen tension coordinates this makes a loop, half of which is ascent and half is descent. Similar loops have been recorded in muscular work, hyperpnea, and hypercapnia [Rahn & Otis (147)]. Further evidence has been presented that for the same inspired oxygen tension, air breathing at low altitude is more advantageous than oxygen breathing at high altitude because of the higher alveolar oxygen tension in the former case (146). The addition of carbon dioxide when pure oxygen is inspired did not improve the tolerance to altitude (134).

Changes in the alveolar gases might also result at altitude if

there is any change in the water vapor. Marshall & Specht (118) have found that actually less water is eliminated from the nose per minute at altitude than at sea level. This was only partly accounted for by a decreased minute volume of ventilation at altitude. Actually their data show that the loss of water in the respiratory gases is only 57 per cent at ground level and 51.3 per cent at altitude of the amount expected if all the air left the body saturated at 37°C. (our calculations). This probably means that the air is cooled and loses water by condensation in the nostrils. The authors reported that frequency of breathing had more effect on the water elimination than the volume, i.e., slower breathing eliminated more water. These experiments do not appear to require modification of the assumption that the air in the alveoli has a vapor pressure of 47 mm.

*Body temperature, oxygen consumption, and cardiac output at altitude.*—At altitude or low oxygen pressures, mice are unable to regulate the body temperature and the body temperature falls. Even in man in a cold environment, shivering is inhibited in the absence of adequate oxygen supply and there is some fall in rectal temperature [Kottke *et al.* (102)]. In rats, for each altitude there is a characteristic fall in body temperature which is maintained [Quimby *et al.* (141)]. The fall in rate of oxygen consumption [in guinea pigs, Rothschild (157)] is intensified by a combination of cold and high thyroid intake [Blood *et al.*, in rats (21)]. In man, breathing low oxygen mixtures, even at comfortable temperatures, a rise in oxygen consumption in two out of three subjects (74) has been reported and in a cold environment the body temperature falls in spite of an increased rate of heat production. (197).

An increase in cardiac output at altitude has been again reported in man [Starr & McMichael (179), Wezlar & Frank (196, 197)], and in dogs it has been shown that the increase of venous return is chiefly in the superior rather than the inferior vena cava [Feldman *et al.* (64)].

*Pressure breathing.*—Pressure breathing results in an increase in the size of knee jerks [Elwell & Bean (61)], a loss of fluid from the plasma [Henry *et al.* (90), Hyman & Goodman (97, 98)], a decrease in cardiac output, and a decrease in the alveolar-arterial oxygen tension gradient due to more uniform ventilation of the alveoli [Courmand *et al.* (43), Motley *et al.* (127)]. Clinical applications of pressure breathing have been discussed by Barach (12, 13)

and Ryder & Kehoe (158). From analyses of arterial blood Taylor *et al.* (185) have presented further evidence that the gain in altitude with pressure breathing is determined accurately by the increased alveolar oxygen tension. The advantages of voluntary pressure breathing at altitude have been shown to be due largely to the hyperventilation which accompanies this procedure [Fenn *et al.* (66)].

*Decompression sickness and explosive decompression.*—Decompression sickness is of importance both in aviation and in diving. In the former the incidence of bends has not been found serious in repeated flights to 20,000 feet [Smedal & Graybiel (173)] and some correlation was found between the incidence of bends and the resting systolic blood pressure and respiratory rate [Robinson (154)]. For avoidance of bends in diving the use of hydrogen has been recommended by Bjurstedt (18), and a further study of nitrogen narcosis and other problems of submarine escape has been presented by Donald *et al.* (52). Difficulties due to the fluctuating pressures in submarines using the "snorkel" or "snort" have also been discussed by Ellis (60). Tables for surface decompression in a chamber have also been described (52, 193). A related problem is the study of the rate of removal of gas from the colon by inhalation of oxygen and equilibration with the venous blood [Pogrun & Steggerda (138, 139)]. On account of the interests of the Air Force in the use of pressure cabins a large number of studies have been reported on the physiological effects of explosive decompressions to extreme or moderate altitudes using monkeys, dogs, and men as subjects [Hitchcock *et al.* (28, 29, 92, 100, 101, 188, 189) Gelfan *et al.* (54, 194), Corey (41, 42), Paton (137), and Mahoney (116)].

*Oxygen poisoning.*—A wealth of new data on oxygen poisoning has been reported by Donald *et al.* (52), who show that the same partial pressure of oxygen is uniformly more toxic under water than in a dry chamber. Oxygen at a high pressure of 5.2 atm. has been shown to be less toxic for rats if the rate of oxygen consumption is reduced either by chilling the body or by experimental hypothyroidism [Grossman & Penrod (83, 84)]. Measurements of the gas tensions in the tissues during oxygen poisoning in cats have shown that the carbon dioxide tension rises and the oxygen tension falls [Taylor (184)]. Data on the fall of the subcutaneous and

intraperitoneal oxygen tension in rats at low oxygen pressures have also been provided [see (192)].

*Resuscitation.*—There have been many contributions concerning resuscitation during the year including several reviews or general discussions (6, 105, 136), some reports of individual clinical experiences (3, 114, 119, 159), a description of a new rubber portable Drinker respirator [Lamport & Eichhorn (107)], another of a tracheotomy inhalator device with humidification and positive pressure [Kubicek *et al.* (104)], a study of lung pathology after resuscitation in infants and the possible usefulness of intravenous hydrogen peroxide in animals including man with low blood catalase activity [Lorincz *et al.* (113), Schwab *et al.* (168)]. Two additional studies of diffusion respiration have been published in which the lungs are filled with oxygen and the carbon dioxide is allowed to accumulate without any respiratory movements [Whitehead *et al.* (198), Parry *et al.* (135)]. A new method called electrophrenic respiration has also been described by Whittenberger, Sarnoff and others (161 to 165, 199). In this method the phrenic nerve is stimulated electrically, and it is shown that the resulting contractions of the diaphragm are sufficient to cause an adequate pulmonary ventilation. The experiments have brought out also a number of interesting points concerning the physiology of respiration.

Careful studies of the physiological processes involved in anoxia and asphyxia have been reported for dogs by Swann (181, 182), by Schwerma, Ivy, Friedman *et al.* (169, 170, 171) and for man by Motley, Cournand *et al.* (126). All of these studies agree that mechanical respirators are superior to manual methods and improve the chances of survival. In the dog experiments, whatever the method used for producing the anoxia, the chances of survival were shown to be very small unless the resuscitation was applied very promptly after the cessation of breathing. Addition of carbon dioxide was of no value. Similar results were obtained in drowning experiments in dogs [Fainer *et al.* (63), Swann (182)]. In fresh water drowning the blood is diluted and in salt water it is concentrated (182). Data on the oxygen content of the blood or lungs when breathing stops have also been reported [Stacey *et al.* (177), Binet & Strumza (16, 17)]. Different methods of artificial respiration have further been studied in conscious human subjects [Spiro *et al.* (175)] and in rats [Blood & D'Amour 20)]. Thompson

(186) has demonstrated by radioactive tracers that alternating positive and negative pressures in the lungs do cause some circulation of the blood even in dead dogs.

*Methods.*—Some of the more important new methods and apparatus described during the past year include a mass spectrometer for continuous and simultaneous analysis of oxygen, carbon dioxide, and nitrogen [Hunter, Stacy & Hitchcock (95)], a rapid and continuous infrared analyzer for carbon dioxide and certain other gases (Fowler, 70, 71), an infrared carbon dioxide analyzer and automatic alveolar air sampling device for application to small animals [Blinn & Noell (19)], and a portable infrared carbon dioxide analyzer for human metabolic studies in the field (Spoor, 176).

#### ADDITIONAL STUDIES OF RESPIRATION NOT REVIEWED IN DETAIL

Available space has precluded detailed consideration of a large number of meritorious contributions. Some of them are listed in the following paragraphs.

*Anoxia effects.*—The influence of anoxia on the following physiological mechanisms has been studied: circulation (201, 202, 203), central nervous system (204 to 210), and kidney (219 to 224). In addition, the changes in blood chemistry (211 to 218) and in histological structure of tissues (225 to 228) have been investigated. There are also certain general studies of anoxia effects (229 to 234). A number of workers have been interested in clinical tests involving anoxia (235 to 241), in the anoxia accompanying clinical pulmonary insufficiency (242 to 245), in the clinical use of the ear oximeter in blood saturation studies (246 to 272), in oxygen and nitrogen therapy (273 to 280), and in carbon monoxide poisoning (281 to 293).

*Carbon dioxide effects.*—The influence of carbon dioxide on the circulation (294 to 298), nervous system (299 to 307), and miscellaneous functions (308, 309) has been considered.

*Lung volumes and respiratory mechanics.*—Aspects of this topic concerning which reports have become available include: anatomy and histology of the respiratory system (329 to 333), drug effects (334 to 344), retention of aerosols and dust (345 to 349), circulation (350, 351, 352), and miscellaneous (353 to 359).

*Drug effects.*—The influence of various drugs on the chemore-

ceptors (310, 311, 312) and on ventilation (313 to 317) has been investigated.

*Experimental pulmonary disorders.*—Reports of the experimental production of pulmonary edema (318 to 326) and of pulmonary embolism (327, 328) have been published.

*Methods.*—Methods for study of the following have been described: gas analysis (360 to 367), alveolar gas sampling (368 to 371), recording of volume and frequency of respiration (372 to 377), oxygen consumption of small animals (378 to 381), and miscellaneous techniques of use in respiratory physiology (382 to 385).

#### LITERATURE CITED

1. ALTLAND, P. D., *Federation Proc.*, **8**, 3 (1949)
2. AMENT, R., SUSKIND, M., AND RAHN, H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 401-6 (1949)
3. ARDITI, J., *La Prensa. méd. Arg.*, **35**, 1878 (1948)
4. ARSHAVSKI, I. A., *J. Physiol. U.S.S.R.*, **34**, 61-70 (1948)
5. ASMUSSEN, E., AND NIELSEN, M., *Acta Physiol. Scand.*, **16**, Suppl. 53, 3-4 (1948)
6. AUSHERMAN, H. M., *Anesthesia & Analgesia*, **27**, 172-75 (1948)
7. AVIADO, D. M., AND PONTIUS, R. G., *Federation Proc.*, **8**, 5 (1949)
8. BAARSMA, P. R., AND DIRKEN, M. N. J., *J. Thoracic Surg.*, **17**, 238-51 (1948)
9. BAARSMA, P. R., DIRKEN, M. N. J., AND HUIZINGA, E., *J. Thoracic Surg.*, **17**, 252-63 (1948)
10. BAKOS, A. C. P., AND HOWELL, W. L., *Science*, **108**, 45-46 (1948)
11. BANCROFT, R. W., *Am. J. Physiol.*, **156**, 158-62 (1949)
12. BARACH, A. L., *Physiologic Therapy in Respiratory Diseases*, 408 pp. (J. B. Lippincott Co., Philadelphia 1948)
13. BARACH, A. L., AND BROOKS, J. W., *Bull. U. S. Army Med. Dept.*, **8**, 524-34, 602-12, 703-12, 770-73 (1948)
14. BERG, W. E., *Am. J. Physiol.*, **152**, 465-69 (1948)
15. BINET, L., AND BURNSTEIN, M., *J. franc. méd. et chir. thorac.*, **2**, 101-22 (1948)
16. BINET, L., AND STRUMZA, M. V., *Compt. rend. soc. biol.*, **143**, 44 (1949)
17. BINET, L., AND STRUMZA, M. V., *Compt. rend. soc. biol.*, **143**, 45-46 (1949)
18. BJURSTEDT, H., AND SEVERIN, G., *Military Surgeon*, **103**, 107-16 (1948)
19. BLINN, K. A., AND NOELL, W. K., *Proc. Soc. Exptl. Biol. Med.*, **71**, 141-44 (1949)
20. BLOOD, F. R., AND D'AMOUR, F. E., *Am. J. Physiol.*, **156**, 52-61 (1949)
21. BLOOD, F. R., GLOVER, R. M., HENDERSON, J. B., AND D'AMOUR, F. E., *Am. J. Physiol.*, **156**, 62-66 (1949)
22. BONSDORFF, E., *Acta Physiol. Scand.*, **16**, Suppl. 53, 8 (1948)
23. BOOTHBY, W. M., LUNDIN, G., AND HELMHOLZ, H. F., *Acta Physiol. Scand.*, **16**, Suppl. 53, 9 (1948); *Proc. Soc. Exptl. Biol. Med.*, **67**, 558 (1948)
24. BORDEN, C., WILSON, R. H., AND EBERT, R. V., *J. Lab. Clin. Med.*, **33**, 1453 (1948)

25. BORISON, H. L., *Am. J. Physiol.*, **154**, 55-62 (1948)
26. BROOKS, M. M., *J. Aviation Med.*, **19**, 298-99 (1948)
27. BROWN, E. B., CAMPBELL, G. S., JOHNSON, M. N., HEMINGWAY, A., AND VISSCHER, M. B., *J. Applied Physiol.*, **1**, 333-38 (1948)
28. BURCH, B. H., *Federation Proc.*, **8**, 19 (1949)
29. BURCH, B. H., AND HITCHCOCK, F. A., *Am. J. Physiol.*, **155**, 429 (1948)
30. CALDER, R. M., *Proc. Soc. Exptl. Biol. Med.*, **68**, 642 (1948)
31. CAMPBELL, G. S., BROWN, E. B., AND GOLLAN, F., *Am. J. Physiol.*, **154**, 185-87 (1948)
32. CAMPBELL, G. S., HADDY, F. J., AND VISSCHER, M. B., *Proc. Soc. Exptl. Biol. Med.*, **71**, 52-54 (1949)
33. CHATFIELD, P. O., AND MEAD, S., *Am. J. Physiol.*, **154**, 417-22 (1948)
34. CHEYMOL, J., *J. physiol.*, **40**, 146A-47A (1948)
35. CHIODI, H., *Acta Med. Scand.*, **131**, 403-16 (1948)
36. CHIODI, H., FASCILOLO, J. C., SUÁREZ, J. R. E., AND TAQUINI, A. C., *J. Applied Physiol.*, **1**, 148-56 (1948)
37. CHURCHILL, E. D., *J. Thoracic Surg.*, **18**, 279-93 (1949)
38. COLDAHL, H., *Acta Med. Scand.*, **132**, 378-83 (1949)
39. CORDIER, D., AND CORDIER, G., *J. physiol.*, **40**, 155A-57A (1948)
40. CORDIER, D., AND CORDIER, G., *J. physiol.*, **40**, 158A-59A (1948)
41. COREY, E. L., *Federation Proc.*, **8**, 29 (1949)
42. COREY, E. L., *Am. J. Physiol.*, **157**, 88-93 (1949)
43. COUNNAND, A., MOTLEY, H. L., WERKO, L., AND RICHARDS, D. W., *Am. J. Physiol.*, **152**, 162-74 (1948)
44. COUNNAND, A., RILEY, R. L., AND HIMMELSTEIN, A., *Federation Proc.*, **8**, 30 (1949)
45. DALY, I. DEB., DUKE, H., HEBB, C. O., AND WEATHERALL, J., *Quart. J. Exptl. Physiol.*, **34**, 285-313 (1948)
46. DEXTER, L., HAYNES, F. W., AND HELLEMS, H. K., *Am. J. Physiol.*, **155**, 433 (1948)
47. DILL, D. B., AND PENROD, K. E., *Am. J. Physiol.*, **155**, 433 (1948)
48. DILL, D. B., AND PENROD, K. E., *J. Applied Physiol.*, **1**, 409-17 (1948)
49. DIRKEN, M. N. J., AND HEEMSTRA, H., *Quart. J. Exptl. Physiol.*, **34**, 193-211 (1948)
50. DIRKEN, M. N. J., AND HEEMSTRA, H., *Quart. J. Exptl. Physiol.*, **34**, 213-26 (1948)
51. DIRKEN, M. N. J., AND HEEMSTRA, H., *Quart. J. Exptl. Physiol.*, **34**, 227-41 (1948)
52. DONALD, K. W., DAVIDSON, W. M., AND SHELFORD, W. O., *J. Hyg.*, **46**, 176-83 (1948)
53. DOUGLAS, J. C., RILEY, R. L., AND COUNNAND, A., *Federation Proc.*, **8**, 36 (1949)
54. DOWLING, R., AND GELFAN, S., *Federation Proc.*, **8**, 36 (1949)
55. DRINKER, C. K., *Am. Rev. Tuberc.*, **58**, 1-14 (1948)
56. DUKE, H. N., *J. Physiol. (London)*, **108**, 59 (1949)
57. DUKE, H. N., *Quart. J. Exptl. Physiol.*, **35**, 25-37 (1949)
58. ECKENHOFF, J. E., AND HAFKENSCHIEL, J. H., *Am. Heart J.*, **36**, 893-98 (1948)

59. EDITORIAL, *J. Am. Med. Assoc.*, **136**, 417 (1948)
60. ELLIS, F. P., *Brit. J. Ind. Med.*, **6**, 24-30 (1949)
61. ELWELL, L. H., AND BEAN, J. W., *Federation Proc.*, **8**, 41 (1949)
62. EULER, U. S. V., AND LILJESTRAND, G., *Acta Physiol. Scand.*, **16**, Suppl. 53, 21 (1948)
63. FAIRER, D. C., MARTIN, C. G., SCHWERMA, H., AND IVY, A. G., *Federation Proc.*, **8**, 43 (1949)
64. FELDMAN, M., JR., ROBBARD, S., AND KATZ, L. N., *Am. J. Physiol.*, **154**, 391-96 (1948)
65. FENN, W. O., *Proc. Am. Phil. Soc.*, **92**, 144-54 (1948)
66. FENN, W. O., RAHN, H., OTIS, A. B., AND CHADWICK, L. E., *J. Applied Physiol.*, **1**, 752-72 (1949)
67. FENN, W. O., RAHN, H., OTIS, A. B., AND CHADWICK, L. E., *J. Applied Physiol.*, **1**, 773-89 (1949)
68. FISET, P. E., AND DUGAL, L. P., *Federation Proc.*, **8**, 45 (1949)
69. FORTIER, C., *Proc. Soc. Exptl. Biol. Med.*, **70**, 76-78 (1949)
70. FOWLER, R. C., *Am. J. Physiol.*, **155**, 436 (1948)
71. FOWLER, R. C., *Rev. Sci. Instruments*, **20**, 175-78 (1949)
72. FOWLER, W. S., *Am. J. Physiol.*, **155**, 437 (1948)
73. FOWLER, W. S., *Am. J. Physiol.*, **154**, 405-16 (1948)
74. FRANK, E., AND WEZLER, K., *Arch. ges. Physiol. (Pflügers)*, **250**, 320-42 (1948)
75. GALDSTON, M., AND HORWITZ, S. A., *Am. J. Physiol.*, **155**, 420-24 (1948)
76. GARDNER, E., AND JACOBS, J., *Am. J. Physiol.*, **153**, 567-79 (1948)
77. GEORG, J., AND SONNE, L. M., *Acta Physiol. Scand.*, **16**, 52-62 (1948)
78. GILSON, J. C., AND HUGH-JONES, P., *Clin. Sci.*, **7**, 185-216 (1949)
79. GRANDJEAN, E., *J. physiol.*, **40**, 51A-96A (1948)
80. GRANDJEAN, E., *Schweiz. med. Wochschr.*, **79**, 515-18 (1949)
81. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *J. physiol.*, **40**, 202A-3A (1948)
82. GRODINS, F. S., AND MORGAN, D. P., *Federation Proc.*, **8**, 61 (1949)
83. GROSSMAN, M. S., AND PENROD, K. E., *Am. J. Physiol.*, **156**, 177-81 (1949)
84. GROSSMAN, M. S., AND PENROD, K. E., *Am. J. Physiol.*, **156**, 182-84 (1949)
85. HALL, F. G., *J. Applied Physiol.*, **1**, 490-95 (1949)
86. HAYTER, R., AND DUFFNER, G. J., *U. S. Naval Med. Bull.*, **48**, 234-39 (1948)
87. HEBB, C., AND NIMMO-SMITH, R. H., *Quart. J. Exptl. Physiol.*, **34**, 159-63 (1948)
88. HEERHABER, I., *Arch. ges. Physiol. (Pflügers)*, **250**, 385-95 (1948)
89. HELLEMS, H. K., HAYNES, F. W., DEXTER, L., AND KINNEY, T. D., *Am. J. Physiol.*, **155**, 98-105 (1948)
90. HENRY, J. P., HENDRICKSON, I., MORITT, E., AND MEEHAN, J. P., *J. Clin. Invest.*, **27**, 700-5 (1948)
91. HESSER, C. M., *Acta Physiol. Scand.*, **18**, Suppl. 64, 1-69 (1949)
92. HITCHCOCK, F. A., WHITEHORN, W. V., AND EDELMANN, A., *J. Applied Physiol.*, **1**, 418-29 (1948)
93. HOFF, E. C., *A Bibliographical Sourcebook of Compressed Air, Diving and Submarine Medicine*, 382 pp. (U. S. Govt. Printing Office, Washington, D. C., 1948)

94. HOFF, H. E., AND BRECKENRIDGE, C. G., *Federation Proc.*, **8**, 76 (1949)
95. HUNTER, J. A., STACY, R. W., AND HITCHCOCK, F. A., *Rev. Sci. Instruments*, **20**, 333-36 (1949)
96. HURTADO, A., AND ASTE-SALAZAR, H., *J. Applied Physiol.*, **1**, 304-25 (1948)
97. HYMAN, C., AND GOODMAN, J., *Am. J. Physiol.*, **155**, 444 (1948)
98. HYMAN, C., AND GOODMAN, J., *Am. J. Physiol.*, **155**, 208-14 (1948)
99. KAADA, B. R., PRIBRAM, K. H., AND EPSTEIN, J. A., *Federation Proc.*, **8**, 83 (1949)
100. KEMPH, J. P., AND HITCHCOCK, F. A., *Am. J. Physiol.*, **155**, 447 (1948)
101. KEMPH, J. P., AND HITCHCOCK, F. A., *Federation Proc.*, **8**, 85 (1949)
102. KOTTKE, F. J., PHALEN, J. S., TAYLOR, C. B., VISSCHER, M. B., AND EVANS, G. T., *Am. J. Physiol.*, **153**, 10-15 (1948)
103. KOTTKE, F. J., TAYLOR, C. B., KUBICEK, W. G., ERICKSON, D. M., AND EVANS, G. T., *Am. J. Physiol.*, **153**, 16-20 (1948)
104. KUBICEK, W. G., HOLT, G. W., ELAM, J. O., BROWN, J. R., AND GULLIKSON, G., *Arch. Phys. Med.*, **29**, 217-25 (1948)
105. KUBICEK, W. G., HOLT, G. W., AND KOTTKE, F. J., *Arch. Phys. Med.*, **29**, 84-88 (1948)
106. LAMBERTSON, C. J., CLARK, J. K., AVIADO, D. M., PONTIUS, R. G., BARKER, E. S., AND MOYER, J., *Federation Proc.*, **8**, 90 (1949)
107. LAMPORT, H., AND EICHHORN, R. D., *Science*, **108**, 288-89 (1948)
108. LARRABEE, M. G., AND HODES, R., *Am. J. Physiol.*, **155**, 147-64 (1948)
109. LAWTON, R. W., AND KING, A. L., *Federation Proc.*, **8**, 92 (1949)
110. LOMBARD, C. F., ROTH, H. P., AND DRURY, D. R., *J. Aviation Med.*, **19**, 355-64 (1948)
111. LO MONACO-CROCE, T., TAGLIAMONTE, B., AND FORTI, L., *Rev. Med. Aeronaut.*, **11**, 337-50 (1948)
112. LONG, J. H., WESTER, M. R., AND OPPENHEIMER, M. J., *J. Thoracic Surg.*, **18**, 269-78 (1949)
113. LORINCZ, A. L., JACOBY, J. J., AND LIVINGSTONE, H. M., *Anesthesiology*, **9**, 162-74 (1948)
114. LYONS, S. S., *J. Mt. Sinai Hosp. N. Y.*, **15**, 240-45 (1948)
115. MACKAY, R. S., *Am. J. Phys.*, **16**, 186-87 (1948)
116. MAHONEY, D. I., *Federation Proc.*, **8**, 104 (1949)
117. MALORNY, G., *Arzliche Wochschr.*, **3**, 636-37 (1948)
118. MARSHALL, L. H., AND SPECHT, H., *Am. J. Physiol.*, **156**, 299-310 (1949)
119. MAUTZ, F. R., BECK, C. S., AND CHASE, H. F., *J. Thoracic Surg.*, **17**, 283-96 (1948)
120. MEETER, E., *Nederland. Tijdschr. Geneesk.*, **92**, 3032-34 (1948)
121. MELLINGER, G. W., Wright Field Rept., MCRFXD-696-112 J, 12 pp. (Air Materiel Command, U. S. Air Force, March 17, 1949)
122. MENEELY, G. R., AND KALTREIDER, N. L., *J. Clin. Invest.*, **28**, 129-39 (1949)
123. MERINO, C. F., AND REYNAFARJE, C., *J. Lab. Clin. Med.*, **34**, 637-47 (1949)
124. MONGE, C., *Acclimatization in the Andes*, 130 pp. (The Johns Hopkins Press, Baltimore, 1948)
125. MORGAN, D. P., AND GRODINS, F. S., *Federation Proc.*, **8**, 113 (1949)
126. MOTLEY, H. L., COURNAND, A., WERKO, L., DRESDALE, D. T., HIMMELSTEIN, A., AND RICHARDS, D. W., JR., *J. Am. Med. Assoc.*, **137**, 370-82 (1948)

127. MOTLEY, H. L., LANG, L. P., AND GORDON, B., *J. Aviation Med.*, **19**, 346-54 (1948)
128. MOTLEY, H. L., LANG, L. P., AND GORDON, B., *Am. Rev. Tuberc.*, **59**, 270-88 (1949)
129. NICHOLS, J., *J. Aviation Med.*, **19**, 171-78 (1948)
130. NORTHUP, D. W., AND BELL, R., *Federation Proc.*, **8**, 120 (1948)
131. OTIS, A. B., *Federation Proc.*, **8**, 122 (1949)
132. OTIS, A. B., *J. Applied Physiol.*, **1**, 743-51 (1949)
133. OTIS, A. B., AND BEMBOWER, W. C., *Am. J. Physiol.*, **155**, 458 (1948)
134. OTIS, A. B., RAHN, H., AND CHADWICK, L. E., *Proc. Soc. Exptl. Biol. Med.*, **71**, 487-90 (1949)
135. PARRY, T. M., SPENCER, J. N., WHITEHEAD, R. W., AND DRAPER, W. B., *Am. J. Physiol.*, **155**, 459 (1948)
136. PASK, E. A., *Proc. Roy. Soc. Med.*, **41**, 138-42 (1948)
137. PATON, W. D. M., *J. Physiol. (London)*, **107**, 1p-2p (1948)
138. POGGRUND, R. S., AND STEGGERDA, F. R., *J. Aviation Med.*, **19**, 204-10 (1948)
139. POGGRUND, R. S., AND STEGGERDA, F. R., *Am. J. Physiol.*, **153**, 475-82 (1948)
140. PRAST, J. W., AND NOELL, W. K., *J. Aviation Med.*, **19**, 426-34 (1948)
141. QUIMBY, F. H., PHILLIPS, N. E., CARY, B. B., AND MORGAN, R., *Am. J. Physiol.*, **155**, 462 (1948)
142. RABINOVITCH, R., ELLIOTT, K. A. C., AND McEACHERN, D., *J. Lab. Clin. Med.*, **33**, 294-96 (1948)
143. RAHN, H., *Am. J. Physiol.*, **155**, 462 (1948)
144. RAHN, H., *Federation Proc.*, **8**, 129 (1949)
145. RAHN, H., FENN, W. O., AND OTIS, A. B., *J. Applied Physiol.*, **1**, 725-36 (1949)
146. RAHN, H., AND OTIS, A. B., *Proc. Soc. Exptl. Biol. Med.*, **70**, 185-86 (1949)
147. RAHN, H., AND OTIS, A. B., *J. Applied Physiol.*, **1**, 717-24 (1949)
148. RAKSHIT, P., *Quart. J. Exptl. Physiol.*, **35**, 47-53 (1949)
149. REED, E. A., AND SCOTT, J. C., *Federation Proc.*, **8**, 130 (1949)
150. REIN, F. H., *Fiat Review of German Science, Part II, Vegetative Physiology* (U. S. Office of Military Govt. for Germany, Economics Division, Research Control Branch, Berlin, Germany, 1947)
151. REYNOLDS, O. E., *Am. J. Physiol.*, **155**, 463 (1948)
152. RIJLANT, P., *Journal de Physiologie*, **40**, 294A-95A (1948)
153. RILEY, R. L., AND Cournand, A., *Federation Proc.*, **8**, 132 (1949)
154. ROBINSON, T. W., *Federation Proc.*, **8**, 133 (1949)
155. ROBBARD, S., AND BROWN, F., *Am. J. Physiol.*, **155**, 464 (1948)
156. ROH, C. E., GREENE, D. G., HIMMELSTEIN, A., HUMPHREYS, G. H., AND BALDWIN, E. D., *Am. J. Med.*, **6**, 795-98 (1949)
157. ROTHSCHUH, K., *Arch. ges. Physiol. (Pflügers)*, **249**, 175-90 (1948)
158. RYDER, H. W., AND KEHOE, R. A., *Anesthesiology*, **9**, 21-31 (1948)
159. SÁNDOR, G., GÁL, I., ADLER, P., AND VEGH, L., *Anesthesia & Analgesia*, **28**, 177-79 (1949)
160. SANTENOISE, D., GRANDPIERRE, R., GUILHEM, J., AND THIÉBLot, L., *J. physiol.*, **40**, 305A-6A (1948)
161. SARNOFF, S. J., *Am. J. Physiol.*, **155**, 466 (1948)

162. SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L., *Science*, **108**, 482-83 (1948)
163. SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L., *Am. J. Physiol.*, **155**, 1-9 (1948)
164. SARNOFF, S. J., MALONEY, J. V., AND WHITTENBERGER, J. L., *Federation Proc.*, **8**, 138 (1949)
165. SARNOFF, S. J., WHITTENBERGER, J. L., AND HARDENBERGH, E., *Am. J. Physiol.*, **155**, 203-7 (1948)
166. SAUNDERS, J. A., *J. Physiol. (London)*, 353-58 (1949)
167. SCHAEFER, K. E. (Ed.), *Symposium on Submarine Medicine*, 836 pp., U. S. Fleet Naval Forces, Germany, Technical Section (Medical)
168. SCHWAB, W., EASTMAN, H. D., AND ETSTEN, B., *N. Y. State J. Med.*, **48**, 1703-8 (1948)
169. SCHWERMA, H., IVY, A. C., BURKHARDT, W. L., AND THOMETZ, A. F., *Am. J. Physiol.*, **156**, 145-48 (1949)
170. SCHWERMA, H., IVY, A. C., FRIEDMAN, H., AND LABROSSE, E., *Occupational Med.*, **5**, 24-48 (1948)
171. SCHWERMA, H., IVY, A. C., AND FRIEDMAN, H., *J. Applied Physiol.*, **1**, 157-68 (1948)
172. SCOTT, J. C., REED, E. A., SARIS, D., AND REDONDO RAMIREZ, H. P., *Am. J. Physiol.*, **154**, 428-32 (1948)
173. SMEDAL, H. A., AND GRAYBIEL, A., *J. Aviation Med.*, **19**, 253-69 (1948)
174. SMITH, P. K., *Am. J. Med.*, **4**, 645-48 (1948)
175. SPIRO, R. K., GOLTRA, E. R., AND THOMPSON, J. S., *J. Applied Physiol.*, **1**, 285-97 (1948)
176. SPOOR, H. J., *J. Applied Physiol.*, **1**, 369-84 (1948)
177. STACY, R. W., WHITEHORN, W. V., AND HITCHCOCK, F. A., *Am. J. Physiol.*, **153**, 87-92 (1948)
178. STANNARD, J. N., AND RUSS, E. M., *J. Applied Physiol.*, **1**, 326-32 (1948)
179. STARR, I., AND McMICHAEL, M., *J. Applied Physiol.*, **1**, 430-40 (1948)
180. STEPHEN, C. R., *Anesthesiology*, **9**, 134-40 (1948)
181. SWANN, H. G., *Studies in Resuscitation* MCREXD-696-79 G, p. 128, Air Materiel Command, U. S. Air Force (1949)
182. SWANN, H. G., *Studies in Resuscitation* MCREXD-696-79 J., 89 pp., Air Materiel Command, U. S. Air Force (1949)
183. SWAN, H., AND MULLIGAN, R. M., *J. Thoracic Surg.*, **17**, 44-56 (1948)
184. TAYLOR, H. J., *J. Physiol. (London)*, **108**, 264-69 (1949)
185. TAYLOR, C. B., MARBARGER, J. P., AND POWER, M. H., *J. Applied Physiol.*, **1**, 45-52 (1948)
186. THOMPSON, S. A., *J. Thoracic Surg.*, **17**, 323-34 (1948)
187. TRUETA, J., *Yale J. Biol. Med.*, **21**, 1-16 (1948)
188. VAIL, E. G., AND HITCHCOCK, F. A., *Am. J. Physiol.*, **155**, 473 (1948)
189. VAIL, E. G., AND HITCHCOCK, F. A., *Federation Proc.*, **8**, 168 (1949)
190. VAN GOOR, H., *Enzymologia*, **13**, 73-164 (1948)
191. VERLOOP, M. C., *Acta Anatomica*, **7**, 1-32 (1949)
192. VERZAR, F., *Höhenklima-Forschungen des Basler Physiologischen Institutes*, **2**, 1-97 (B. S. Schwabe and Co., Basel, 1948)
193. VON DÖBELN, W., *Acta Physiol. Scand.*, **16**, Suppl. 53, 17 (1948)

194. WERNER, A. Y., AND GELFAN, S., *Federation Proc.*, **8**, 163 (1949)
195. WETERLINGS, P. A. A., *Acta Med. Scand.*, **130**, 232-58 (1948)
196. WEZLER, K., AND FRANK, E., *Arch. ges. Physiol. (Pflügers)*, **250**, 249-76 (1948)
197. WEZLER, K., AND FRANK, E., *Arch. ges. Physiol. (Pflügers)*, **250**, 439-64 (1948)
198. WHITEHEAD, R. W., SPENCER, J. N., PARRY, T. M., AND DRAPER, W. B., *Anesthesiology*, **10**, 54-60 (1949)
199. WHITTENBERGER, J. L., SARNOFF, S. J., AND HARDENBERGH, E., *J. Clin. Invest.*, **28**, 124-28 (1949)
200. WILLMON, T. L., AND BEHNKE, A. R., *Am. J. Physiol.*, **153**, 138-42 (1948)

## ADDITIONAL REFERENCES

201. FELDMAN, M., JR., RODBARD, S., AND KATZ, L. N., *Am. J. Physiol.*, **154**, 391-96 (1948)
202. NOELL, W., AND SCHNEIDER, M., *Arch. ges. Physiol. (Pflügers)*, **250**, 35-41 (1948)
203. VAN LOO, A., SURTSHIN, A., AND KATZ, L. N., *Am. J. Physiol.*, **154**, 397-404 (1948)
204. BEYNE, J., AND CHAUCHARD, P., *J. physiol.*, **40**, 113A-14A (1948)
205. FENN, W. O., GALAMBOS, R., OTIS, A. B., AND RAHN, H., *J. Applied Physiol.*, **1**, 710-16 (1949)
206. GANTT, W. H., THORN, G. W., AND DORRANCE, C., *Federation Proc.*, **8**, 53 (1949)
207. GELLHORN, E., *Arch. Phys. Med.*, **29**, 88-91 (1948)
208. NOELL, W. K., AND CHINN, H. I., *Federation Proc.*, **8**, 119 (1949)
209. RÉMOND, A., *Rev. neurol.*, **80**, 579-88 (1948)
210. STOKES, J., 3rd, CHAPMAN, W. P., AND SMITH, L. H., *J. Clin. Invest.*, **27**, 299-304 (1948)
211. BINET, L., AND STRUMZA, M. V., *Compt. rend. soc. biol.*, **143**, 45-46 (1949)
212. BURKHARDT, W. L., FLICKINGER, D., AND ADLER, H. F., *Federation Proc.*, **8**, 19 (1949)
213. LOESCHKE, G., AND LOESCHKE, H. H., *Arch. ges. Physiol. (Pflügers)*, **249**, 521-38 (1948)
214. STICKNEY, J. C., NORTHUP, D. W., AND VAN LIERE, E. J., *Am. J. Physiol.*, **154**, 423-27 (1948)
215. SUSCA, L. A., *Federation Proc.*, **8**, 152 (1949)
216. TEPPERMAN, J., AND TEPPERMAN, H., *J. Clin. Invest.*, **27**, 176-86 (1948)
217. VAN LIERE, E. J., STICKNEY, J. C., AND NORTHUP, D. W., *Am. J. Physiol.*, **155**, 10-14 (1948)
218. VAN MIDDLESWORTH, L., *Federation Proc.*, **8**, 158 (1949)
219. BRYAN, A. H., AND RICKETTS, H. T., *Committee on Aviation Med.*, Rept. 145, July 19, 1943
220. CALDWELL, F. T., ROLF, D., AND WHITE, H. L., *J. Applied Physiol.*, **1**, 597-600 (1949)
221. KELLEY, V. C., AND McDONALD, R. K., *Am. J. Physiol.*, **154**, 201-6 (1948)
222. KLEINSCHMIDT, K., *Arch. ges. Physiol. (Pflügers)*, **250**, 79-90 (1948)
223. McDONALD, R. K., AND KELLEY, V. C., *Am. J. Physiol.*, **154**, 193-200 (1948)

224. VAN MIDDLESWORTH, L., BANNER, R. L., LAWSON, F., AND COX, E. M., *Proc. Soc. Exptl. Biol. Med.*, **69**, 288-90 (1948)
225. ASCHAN, G. K., *Acta Oto-Laryngolog.*, Suppl. No. **69**, 1-93 (1948)
226. CHORNYAK, J., *Bull. U. S. Army Med. Dept.*, **8**, 695-702 (1948)
227. LEWIS, R. B., AND HAYMAKER, W., *J. Aviation Med.*, **19**, 306-36 (1948)
228. METZ, B., *Federation Proc.*, **8**, 109 (1949)
229. BOWEN, W. J., *Federation Proc.*, **8**, 14 (1949)
230. POEL, W. E., *Am. J. Physiol.*, **156**, 44-51 (1949)
231. SMITH, W. W., DOOLEY, R., AND THOMPSON, E. C., *J. Aviation Med.*, **19**, 227-37 (1948)
232. SPICER, S. S., AND NEAL, P. A., *J. Pharmacol. Exptl. Therap.*, **95**, 438-43 (1949)
233. SURTSHIN, A., ROBBARD, S., AND KATZ, L. N., *Am. J. Physiol.*, **152**, 623-32 (1948)
234. VAN LIERE, E. J., CRABTREE, W. V., NORTHUP, D. W., AND STICKNEY, J. C., *Proc. Soc. Exptl. Biol. Med.*, **67**, 331-32 (1948)
235. TIFFENEAU, R., *Bull. acad. med. (Paris)* **132**, 389-91 (1948)
236. BIÖRCK, G., JACKSON, F. S., AND ROHLIN, S., *Acta Med. Scand.*, **132**, 283-301 (1948)
237. BURCHELL, H. B., PRUITT, R. D., AND BARNES, A. R., *Am. Heart J.*, **36**, 373-89 (1948)
238. HOLBROOK, A. A., AND SHAPIRO, H. H., *Wisconsin Med. J.*, **47**, 571-82 (1948)
239. LIPTON, B., AND GIBBS, F. A., *Diseases Nervous System*, **9**, 135-40 (1948)
240. MALMSTROM, G., *Acta Med. Scand.*, **133**, 68-71 (1949)
241. STEWART, H. J., HORGER, E. L., AND SORENSEN, C. W., *Am. Heart J.*, **36**, 161-83 (1948)
242. BALDWIN, E. DE F., COUNNAND, A., AND RICHARDS, D. W., JR., *Medicine*, **28**, 201-37 (1949)
243. HOUSTON, C. S., *New Engl. J. Med.*, **240**, 683-85 (1949)
244. MOTLEY, H. L., AND LANG, L. P., *Federation Proc.*, **8**, 114 (1949)
245. TAQUINI, A. C., FASCIOLLO, J. C., SUAREZ, J. R., AND CHIODI, H., *Arch. Internal. Med.*, **82**, 534-77 (1948)
246. BEHRMANN, V. G., HARTMAN, F. W., ZIEGLER, R. F., AND LAM, C. R., *Federation Proc.*, **8**, 9 (1949)
247. BURCHELL, H. B., AND WOOD, E. H., *Am. J. Physiol.*, **155**, 429 (1948)
248. BURCHELL, H. B., AND WOOD, E. H., *J. Applied Physiol.*, **1**, 560-66 (1949)
249. BURCHELL, H. B., TAYLOR, B. E., KNUTSON, J. R., AND WOOD, E. H., *Federation Proc.*, **8**, 19 (1949)
250. COMROE, J. H., JR., AND WALKER, P., *Am. J. Physiol.*, **152**, 365-71 (1948)
251. DOUGLAS, J. C., AND EDHOLM, O. G., *Am. J. Physiol.*, **155**, 434 (1948)
252. ELAM, J. O., EHRENHAFT, J. L., ELAM, W. N., JR., AND WHITE, H. L., *Federation Proc.*, **8**, 40 (1949)
253. ELAM, J. O., ROOS, A., AND NEVILLE, J. F., JR., *Am. J. Physiol.*, **155**, 435 (1948)
254. ELAM, J. O., HEMINGWAY, A., GULLICKSON, G., AND VISSCHER, M. B., *Arch. Internal. Med.*, **81**, 649-65 (1948)
255. FERGUSON, J. K. W., FINLAYSON, D. M., AND HILLIARD, I. M., *Federation Proc.*, **8**, 44 (1949)

256. FOWLER, W. S., AND COMROE, J. H., JR., *J. Clin. Invest.*, **27**, 327-34 (1948)
257. GODFREY, L., POND, H. S., AND WOOD, F. C., *Am. J. Med. Sci.*, **216**, 605-18 (1948)
258. GOODRICH, B. E., BEHRMANN, V. G., AND HARTMAN, F. W., *J. Lab. Clin. Med.*, **33**, 1454 (1948)
259. GULLICKSON, G., JR., AND HEMINGWAY, A., *Archives Phys. Med.*, **29**, 632-36 (1948)
260. ISSEKUTZ, B., JR., HETÉNYI, G., JR., AND FEUER, I., *J. Physiol. (London)*, **108**, 9-11 (1949)
261. KERGIN, F. G., BEAN, D. M., AND PAUL, W., *J. Thoracic Surg.*, **17**, 709-11 (1948)
262. KNUTSON, J., TAYLOR, B. E., AND WOOD, E. H., *Federation Proc.*, **8**, 87 (1949)
263. MCCracken, W. J., *Federation Proc.*, **8**, 101 (1949)
264. MONTGOMERY, G. E., WOOD, E. H., BURCHELL, H. B., DRY, T. J., PARKER, R. L., AND HELMHOLTZ, H. F., JR., *Am. Heart J.*, **36**, 668-82 (1948)
265. NEVILLE, J. F., JR., ELAM, J. O., SUGIOKA, K., AND ROOS, A., *Federation Proc.*, **8**, 118 (1949)
266. PRESTON, S. N., AND ORDWAY, N. K., *Am. J. Physiol.*, **15**, 696-702 (1948)
267. SLEATOR, W., JR., ELAM, J. O., KILIAN, D. J., AND ELAM, W. N., JR., *Federation Proc.*, **8**, 147 (1949)
268. WASSERMAN, L. R., DOBSON, R. L., AND LAWRENCE, J. H., *J. Clin. Invest.*, **28**, 60-65 (1949)
269. WOOD, E. H., *Am. J. Physiol.*, **155**, 478 (1948)
270. WOOD, E. H., *J. Applied Physiol.*, **1**, 567-74 (1949)
271. WOOD, E. H., TAYLOR, B. E., AND KNUTSON, J., *Federation Proc.*, **8**, 171 (1949)
272. WOOD, E. H., AND GERACI, J. E., *J. Lab. Clin. Med.*, **34**, 387-401 (1949)
273. BACH, W., *Nervenarzt*, **19**, 449-63 (1948)
274. BINET, L., AND STRUMZA, M. V., *Presse méd.*, **56**, 576-77 (1948)
275. DAVIS, C. N., AND ROBERTSON, H. F., *Quart. J. Studies Alc.*, **10**, 59-62 (1949)
276. GORDON, E. E., DARLING, R. C., AND SHEA, E., *Arch. Phys. Med.*, **30**, 154-62 (1949)
277. ONG, S. G., *Ann. inst. Pasteur*, **76**, 415-18 (1949)
278. PRESTON, S. N., AND ORDWAY, N. K., *Am. J. Physiol.*, **152**, 696-702 (1948)
279. TARAN, L. M., AND SZILAGYI, N., *Am. J. Med.*, **5**, 392-401 (1948)
280. TARAN, L. M., AND SZILAGYI, N., *Am. J. Med.*, **5**, 379-91 (1948)
281. BJERVER, K., AND GOLDBERG, L., *Quart. J. Studies Alc.*, **9**, 329-52 (1948)
282. CLARK, R. T., STANNARD, J. N., AND FENN, W. O., *Am. J. Physiol.*, **155**, 430 (1948)
283. CLARK, R. T., STANNARD, J. N., AND FENN, W. O., *Federation Proc.*, **8**, 26 (1949)
284. CLARK, R. T., STANNARD, J. N., AND FENN, W. O., *Science*, **109**, 615-16 (1949)
285. GORBATOW, O., AND NORO, L., *Acta Physiol. Scand.*, **15**, 77-87 (1948)
286. KILLICK, E. M., *J. Physiol. (London)*, **107**, 27-44 (1948)
287. LUMIO, J. S., *Acta Oto-laryngol.*, Suppl. No. **71**, 1-112 (1948)
289. MEIGS, J. W., *Bull. U. S. Army Med. Dept.*, **8**, 542-46 (1948)

290. SCHWERMA, H., IVY, A. C., AND FRIEDMAN, H., *J. Applied Physiology*, **1**, 364-68 (1948)
291. SCHWERMA, H., WOLMAN, W., SIDWELL, A. E., JR., AND IVY, A. C., *J. Applied Physiology*, **1**, 350-63 (1948)
292. SJOSTRAND, T., *Acta Physiol. Scand.*, **15**, 351-61 (1948)
293. TROSTDORF, E., *Nervenarzt*, **18**, 557-61 (1947)
294. GURDJIAN, E. S., WEBSTER, J. E., AND STONE, W. E., *Am. J. Physiol.*, **155**, 191-94 (1948)
295. KETY, S. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 484-92 (1948)
296. LITTLE, W. J., AVERA, J. W., AND HOOBLER, S. W., *Federation Proc.*, **8**, 98 (1949)
297. SPENCER, J. N., GOLDENSOHN, E. S., WHITEHEAD, R. W., GROVER, R. F., AND DRAPER, W. B., *Federation Proc.*, **8**, 149 (1949)
298. VAN MIDDLESWORTH, L., AND KLINE, R. F., *Am. J. Physiol.*, **152**, 22-26 (1948)
299. BAUDOUIN, A., RÉMOND, A., AND DELARUE, R., *Rev. neurol.*, **80**, 615-16 (1948)
300. GYARFAS, K., POLLOCK, G. H., AND STEIN, S. N., *Proc. Soc. Exptl. Biol. Med.*, **70**, 292-93 (1949)
301. MEDUNA, L. J., *J. Nervous Mental Disease*, **108**, 373-79 (1948)
302. MEDUNA, L. J., AND GYARFAS, K., *Diseases Nervous System*, **10**, 3-7 (1949)
303. POLLOCK, G. H., STEIN, S. N., AND GYARFAS, K., *Proc. Soc. Exptl. Biol. Med.*, **70**, 291-92 (1949)
304. SHANES, A. M., *Am. J. Physiol.*, **153**, 93-108 (1948)
305. SILVER, M. L., *Science*, **108**, 685-86 (1948)
306. SILVER, M. L., AND POLLOCK, G. H., *Am. J. Physiol.*, **154**, 439-42 (1948)
307. STEIN, S. N., AND POLLOCK, G. H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 290-91 (1949)
308. MCCLELLAN, W. S. AND COMSTOCK, C. R., JR., *Arch. Phys. Med.*, **30**, 29-36 (1949)
309. STICKNEY, J. C., NORTHUP, D. W., AND VAN LIERE, E. J., *Am. J. Physiol.*, **155**, 471 (1948)
310. BOOKER, W. M., MOLANO, P. A., AND FRENCH, D. M., *Anesthesia & Analgesia*, **28**, 121-29 (1949)
311. DUSTIN, E., AND MAISON, G., *Proc. Soc. Exptl. Biol. Med.*, **67**, 435-37 (1948)
312. FARBER, H. R., YIENGST, M. J., AND SHOCK, N. W., *Am. J. Med. Sci.*, **217**, 256-62 (1949)
313. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *J. Physiol.*, **40**, 199A-201A (1948)
314. HEYMANS, C., DELAUNOIS, A. L., AND JACOB, J., *Arch. Intern. pharmacodynamie*, **75**, 392-401 (1948)
315. LUNDHOLM, L., *Acta Physiol. Scand.*, **16**, 345-66 (1948)
316. MCCANN, J. C., *Anesthesia & Analgesia*, **27**, 314-25 (1948)
317. MOE, G. K., CAPO, L. R., AND PERALTA, R. B., *Am. J. Physiol.*, **153**, 610-15 (1948)
318. CAMPBELL, G. S., AND VISSCHER, M. B., *Am. J. Physiol.*, **157**, 130-34 (1949)
319. DRINKER, C. K., AND HARDENBERGH, E., *Am. J. Physiol.*, **156**, 35-43 (1949)

320. GIBBON, M. H., BRUNER, H. D., BOCHE, R. D., AND LOCKWOOD, J. S., *J. Thoracic Surg.*, **17**, 264-73 (1948)
321. KOENIG, H., AND KOENIG, R., *Proc. Soc. Exptl. Biol. Med.*, **70**, 375-80 (1949)
322. PAINE, R., HOWARD, F. A., BUTCHER, H. R., AND SMITH, J. R., *Federation Proc.*, **8**, 123 (1949)
323. STONE, C. A., AND LOEW, E. R., *Proc. Soc. Exptl. Biol. Med.*, **71**, 122-26 (1949)
324. SURTSHIN, A., KATZ, L. N., AND RODBARD, S., *Am. J. Physiol.*, **152**, 589-90 (1948)
325. SUSSMAN, A. H., HEMINGWAY, A., AND VISSCHER, M. B., *Am. J. Physiol.*, **152**, 585-88 (1948)
326. WAUD, R. A., AND HORNER, R., *Can. J. Research*, **26**, 167-73 (1948)
327. CHAPMAN, D. W., GUGLE, L. J., AND WHEELER, P. W., *Arch. Internal Med.*, **83**, 158-63 (1949)
328. HOLDEN, W. D., SHAW, B. W., CAMERON, D. B., SHEA, P. J., AND DAVIS, J. H., *Surg. Gynecol. Obstet.*, **88**, 23-30 (1949)
329. BERG, R. M., BOYDEN, E. A., AND SMITH, F. R., *J. Thoracic Surg.*, **18**, 216-36 (1949)
330. DEBUSSCHER, G., *Bull. histol. appl. physiol. et path. et tech. microscop.*, **25**, 183-86 (1948)
331. LANTUEJOUL, P., RIBADEAU-DUMAS, L., AND HERAUX, J., *franc. mtd. et chir. thorac.*, **2**, 265-68 (1948)
332. SMITH, F. R., AND BOYDEN, E. A., *J. Thoracic Surg.*, **18**, 195-215 (1949)
333. SMYTH, N. P. D., *Irish J. Med. Sci.*, **6**, 62-70 (1949)
334. BANISTER, J., AND HEBB, C. O., *J. Physiol. (London)*, **108**, 16 (1949)
335. CURRY, J. J., FUCHS, J. E., AND LEARD, S. E., *J. Allergy*, **20**, 104-10 (1949)
336. CURRY, J. J., AND LEARD, S. E., *J. Lab. Clin. Med.*, **33**, 585-94 (1948)
337. CURRY, J. J., AND LOWELL, F. C., *J. Allergy*, **19**, 9-18 (1948)
338. DAUTREBANDE, L., ALFORD, W. C., HIGHMAN, B., DOWNING, R., AND WEAVER, F. L., *J. Applied Physiol.*, **1**, 339-49 (1948)
339. LEVY, L., AND SEABURY, J. H., *J. Allergy*, **19**, 58-61 (1948)
340. LOWELL, F. C., AND SCHILLER, I. W., *J. Allergy*, **19**, 100-7 (1948)
341. OBEL, N. J., AND SCHMITERLÖW, C. G., *Acta Physiol. Scand.*, Suppl. **16**, 51 (1948)
342. SEGAL, M. S., BEAKEY, J. F., BRESNICK, E., AND LEVINSON, L., *J. Allergy*, **20**, 97-103 (1949)
343. TIFFENEAU, R., *Bull. acad. nationale mtd.*, **132**, 389-91 (1948)
344. TUFT, L., AND BLUMSTEIN, G. I., *J. Allergy*, **19**, 288-97 (1948)
345. HATCH, T., AND HEMEON, W. C. L., *J. Ind. Hyg. Toxicol.*, **30**, 172-80 (1948)
346. LANDAHL, H. D., AND HERMANN, R. G., *J. Ind. Hyg. Toxicol.*, **30**, 181-88 (1948)
347. LANDAHL, H. D., AND TRACEWELL, T., *J. Ind. Hyg. Toxicol.*, **31**, 55-59 (1949)
348. WILSON, I. B., AND LAMER, V. K., *J. Ind. Hyg. Toxicol.*, **30**, 265-80 (1948)
349. WILSON, H. B., SYLVESTER, G. E., LASKIN, S., LABELLE, C. W., AND STOKINGER, H. E., *J. Ind. Hyg. Toxicol.*, **30**, 319-31 (1948)
350. BATTRO, A., BIDOGLIA, H., PIETRAFESA, E. R., AND LABOURT, F. E., *Am. Heart J.*, **37**, 11-20 (1949)

351. OPDYKE, D. F., AND BRECHER, G. A., *Federation Proc.*, **8**, 121 (1949)
352. SEELY, R. D., *Am. J. Physiol.*, **154**, 273-80 (1948)
353. BRECHT, K., AND FEYER, E., *Arch. ges. Physiol. (Pflügers)*, **250**, 228-42 (1948)
354. VAN DISHOCK, H. A. E., *Acta Oto-Laryngol.*, **36**, 467-69 (1948)
355. HAJDU, I., McDOWALL, J. S., AND SHAFER, A. Z., *J. Physiol. (London)*, **107**, 16 (1948)
356. HUIZINGA, E., *Acta Oto-Laryngol.*, **37**, 131-37 (1949)
357. MITCHINSON, A. G. H., AND YOFFEY, J. M., *J. Anat.*, **82**, 88-92 (1948)
358. ROBIN, I. G., *Proc. Roy. Soc. Med.*, **41**, 151-53 (1948)
359. ROBIN, I. G., *Clin. J. (London)*, **77**, 201-4 (1948)
360. CROWLEY, J. H., FAULCONER, A., JR., AND LUNDY, J. S., *Anesthesia & Analgesia*, **27**, 255-61 (1948)
361. DIRKEN, M. N. J., AND HEEMSTRA, H., *Quart. J. Exptl. Physiol.*, **34**, 181-92 (1949)
362. FAULCONER, A., JR., *Anesthesiology*, **10**, 1-14 (1949)
363. FAULCONER, A., JR., AND LATTERELL, K. E., *Anesthesiology*, **10**, 247-59 (1949)
364. HARGER, R. N., TURRELL, E. S., AND MILLER, J. M., *J. Lab. Clin. Med.*, **34**, 566-81 (1949)
365. MANN, W. B., AND PARKINSON, G. B., *Rev. Sci. Instruments*, **20**, 41-47 (1949)
366. PUCK, T. T., *Rev. Sci. Instruments*, **19**, 16-23 (1948)
367. RYAN, M. T., NOLAN, J., AND CONWAY, E. J., *Biochem. J.*, **42**, IXIV (1948)
368. BARKER, E. S., PONTIUS, R. G., AND AVIADO, D. M., *Federation Proc.*, **8**, 7 (1949)
369. HESSER, C. M., *Acta Physiol. Scand.*, **18**, Suppl. **64**, 1-14 (1949)
370. LAMBIE, C. G., AND MORRISSEY, M. J., *J. Physiol. (London)*, **107**, 14-23 (1948)
371. LESSER, G., GALDSTON, M., AND PRUSS, M., *Federation Proc.*, **8**, 94 (1949)
372. HERXHEIMER, H., *J. Physiol. (London)*, **108**, 39 (1949)
373. PATON, W. D. M., *J. Physiol. (London)*, **108**, 57 (1949)
374. PECK, H. M., AND WALKER, W. S., *J. Lab. Clin. Med.*, **33**, 784-88 (1948)
375. ROBERTS, P. W., AND WIDDAS, W. F., *J. Physiol. (London)*, **108**, 37 (1949)
376. SILVERMAN, L., PLOTKIN, T., AND LEE, G., *Rev. Sci. Instruments*, **19**, 513-26 (1948)
377. SPECHT, H., AND BRUBACH, H. F., *Rev. Sci. Instruments*, **20**, 442-47 (1949)
378. CLAFF, C. L., AND TAHMISIAN, T. N., *J. Biol. Chem.*, **179**, 577-83 (1949)
379. LESTER, D., AND GREENBERG, L. A., *J. Biol. Chem.*, **176**, 53-57 (1948)
380. LILIENTHAL, J. L., JR., ZIERLER, K. L., AND FOLK, B. P., *Bull. Johns Hopkins Hosp.*, **84**, 238-44 (1949)
381. O'CONNOR, R. J., *J. Exptl. Biol.*, **25**, 313-21 (1948)
382. BOWEN, W. J., *Federation Proc.*, **8**, 14 (1949)
383. NORRIS, C. M., LONG, J., AND OPPENHEIMER, M. J., *J. Thoracic Surg.*, **17**, 357-65 (1948)
384. TSAI, C.-C., *Sci. Technology China*, **2**, 8-9 (1949)
385. YOUNG, W. B., *Federation Proc.*, **8**, 173 (1949)

## DIGESTIVE SYSTEM<sup>1</sup>

BY M. I. GROSSMAN

*Department of Clinical Science, University of Illinois, College of Medicine  
Chicago, Illinois*

### REGULATION OF FOOD AND WATER INTAKE

It was the workers in the field of physiological psychology who first pointed out the inadequacy of the older ideas about thirst, hunger, and appetite and showed the need for broad concepts which would take into consideration such diverse factors as total energy and nutrient balance, and learned patterns of behavior. In recent years increasing attention has been directed toward this field and the focus of efforts has been upon the elucidation of the central problem of the regulation of intake to need, considering the phenomena of hunger, appetite, and thirst as just one of the aspects of the general problem. Recently an attempt has been made to formulate some of these concepts [Janowitz & Grossman (1)].

That the gastric hunger contractions may serve as a useful index of the hunger state is illustrated by a study [Sangster, Grossman & Ivy (2)] showing that when the emptying of an oatmeal testmeal was accelerated by liquefying it with diastase, the gastric hunger contractions and the hunger pangs occurred correspondingly earlier. On the other hand, several pieces of evidence have been added to the belief that gastric hunger contractions may under certain circumstances be an unreliable gauge of the state of hunger and appetite. For example, it has been found (Sangster, Grossman & Ivy (3)) that a dose of *d*-amphetamine too small to cause any inhibition of gastric contractions could completely inhibit food intake. Moreover, the absence of gastric hunger contractions which occur at least temporarily after complete vagotomy in human subjects causes a loss of only the hunger pang and leaves the remainder of the symptom complex of hunger unchanged [Grossman & Stein (4)]. Gastric hunger contractions and their associated hunger pangs are therefore but one element, and a dispensable one, in the total pattern of hunger sensations in the conditioned subject.

<sup>1</sup> This review covers literature which appeared during the period June, 1948, to June, 1949.

Goetzl (5, 6) has continued his studies on the relationship of fluctuations in olfactory thresholds to feelings of appetite and satiety. A recent paper by Goetzl's group (5) maintains that in order for sugar to produce satiety and a rise in olfactory threshold it must be both tasted and ingested into the stomach, neither alone is adequate.

Perhaps the most elusive problem in the field of regulation of food intake is the quest for an understanding of the mechanism of the relationship which obviously exists between caloric depletion and hunger on the one hand and repletion and satiety on the other. The essays that have been made in this field indicate: (a) blood levels of sugar and amino acids are not related to normal hunger or satiety and, although hypoglycemia may act as an emergency stimulus for hunger [Janowitz & Ivy (7)], hyperglycemia induced by parenteral administration of glucose does not inhibit food intake in the dog or rat [Janowitz & Grossman (8), Janowitz, Hanson & Grossman (9)] nor does it abolish hunger sensations in man [Janowitz & Ivy (7)]; and (b) a number of factors co-operate to transform the state of hunger into one of satiety. For example, it was found that the introduction of food into the stomach of esophagostomized dogs had to be done at the same time the animal was sham feeding in order for it to cause a significant reduction in the duration of sham feeding [Janowitz & Grossman (10)].

Archdeacon & Allen (11) compared the food and water intake of dogs when the diet was in pellet form and when it was pulverized. They found the ratio of food to water intake to be unaltered by the physical state of the diet.

Towbin (12) reported that sham drinking in esophagostomized dogs is partially inhibited by distending the stomach with a balloon. He believed that this effect could not be produced in vagotomized dogs. Confirming earlier experiments on man, Cizek & Gregersen (13) found that intravenously administered hypertonic sodium chloride solution caused a decrease in the rate of salivary secretion; the parotid gland showed this effect whereas the submaxillary did not.

#### GASTRIC SECRETION

The mechanism of hydrochloric acid formation by the gastric glands, an old classic among physiological problems, has recently

received renewed impetus with the application to it of the methods for studying the metabolism of isolated tissues *in vitro*. A wide interest in the study of hydrochloric acid formation by bits of isolated gastric mucosa is being shown [Edwards & Edwards (14, 15), Coy & Rehm (16)]. The studies carried out by Davies & Crane and their co-workers in Professor Krebs' laboratory at the University of Sheffield would appear to have special significance because of the new concepts they introduce.

Davies (17) found that when the frog's gastric mucosa secretes acid *in vitro* aerobically it also produces an exactly equivalent amount of alkali which is neutralized by carbon dioxide and passes into the nutrient solution as bicarbonate-ions. He also discovered that the ratio of the rate of oxygen uptake to the rate of hydrochloric acid formation was such that it rendered untenable any theory [such as those proposed by Bull & Gray (18) or Conway (19)] in which the hydrogen ions are produced by oxidative degradation of carbohydrate, fat, or protein. Not enough oxygen was consumed per unit of hydrochloric acid formed to provide all the hydrogen ions by such an oxidative mechanism. Davies' view is that the reaction fundamentally concerned in the production of hydrochloric acid is  $\text{H}_2\text{O} \rightarrow \text{H}^+ + \text{OH}^-$ . The hydrogen ions are secreted and the hydroxide ions are neutralized by carbon dioxide and pass into the nutrient medium as bicarbonate ions. This neutralization of hydroxide ion by carbon dioxide is catalyzed by carbonic anhydrase. Thus Davies has been able to assign a specific function to this enzyme which, as has now been known for some time, is present in the parietal cells in high concentration.

Interestingly, it was shown that at high rates of acid secretion not enough carbon dioxide was formed by cellular metabolism to neutralize all of the hydroxide ions formed, so that some carbon dioxide had to be supplied from an external source. In the absence of an external supply of carbon dioxide, the mucosa became damaged and in some cases even perforated, presumably due to the damage done by the accumulation of unneutralized hydroxide ions (20).

It has been known for over a hundred years that a rather large electrical potential difference exists across the stomach wall, the secretory surface being negative. Rehm and his associates have studied this potential and its relation to acid secretion in the dog. They found that during acid secretion the potential difference falls

and the resistance of the mucosa increases. They also showed that when a current from an outside source was passed through the gastric mucosa, secretion of acid was enhanced when the flow of current was in the same direction as the natural potential difference and inhibited when in the opposing direction. All of these findings were confirmed by Crane, Davies & Longmuir (21, 22), who worked with isolated frog mucosa and they have proposed on the basis of these facts that this electrical energy, derived from the metabolic activity of the cell, is used in an electrochemical process which results in a net separation of hydrogen and hydroxide ions. Rehm & Hokin (23) found that the electromotive force of the stomach of the dog can produce a continuous current of about 1 ma. per sq. cm. and that although this is not enough to produce the hydrochloric acid secreted, the current observed is a minimum measurement and more current may be produced but be unmeasurable by the method used. Following the line of reasoning proposed by Davies & Crane, Patterson & Stetten (24) suggested that electron transfer in the parietal cell may be accomplished by a stratification of metabolic enzymes.

Davenport & Jensen (25, 26) have extended *in vitro* studies to the mammalian stomach finding that acid accumulates in the lumen of the excised stomach of the mouse when it is incubated at 38°C. in buffer solution. Addition of glucose increases the rate of acid formation and in one series carbaminoylcholine also stimulated but in a second series it failed to do so. Interestingly, histamine in a concentration of 1 mg. per cent inhibited acid formation, as did thiocyanate, epinephrine, sulfa compounds capable of inhibiting carbonic anhydrase, a preparation of enterogastrone, and the omission of potassium, calcium, or magnesium from the bathing fluid. No correlation between the rate of secretion and the dry weight of the stomach or its content of carbonic anhydrase could be found. Deamination of amino acids apparently is not performed by gastric tissue. Urea does not augment secretion and this speaks against the suggestion which has been made by others that the urease found in the gastric mucosa may be concerned in acid formation. Likewise the suggestion which has been offered concerning the possible participation of pyruvic acid in hydrochloric acid production is not supported by the finding that decidedly less than 1 mole of pyruvic acid is formed for each mole of hydrochloric acid produced.

The stomach of the frog was found to be capable of maintaining a sustained level of acid and pepsin secretion in response to stimulation by histamine and histologically the fact was confirmed that only one cell type can be distinguished and this is apparently capable of secreting both hydrochloric acid and pepsin [Sheldon & Grossman (27)].

Although many lines of evidence supported the idea that a hormone, gastrin, is formed in the stomach and stimulates acid secretion, no crucial physiological experiment proving its existence has been available. It has been found by Grossman, Robertson & Ivy (28), however, that when either the pyloric or the fundic portion of the stomach is subcutaneously autotransplanted, thus severing all nervous paths between the two parts, distention of the pyloric part is still capable of causing acid secretion in the fundic part. Since only a blood borne substance could account for this effect, we interpret this experiment as constituting crucial proof for the existence of gastrin. Woodward and co-workers (29) confirmed former reports to the effect that resection of the pyloric antrum significantly reduces the secretory response to a test meal in dogs with Pavlov pouches.

Using gastric fistula dogs Jögi & Uvnäs (30) found that chloralose depressed while nembutal, ether, or morphine abolished the gastric secretory response to insulin hypoglycemia. They also recorded the interesting observation that they were unable to stimulate acid secretion in cats by injecting insulin. Jögi, Ström & Uvnäs (31) went on to study the effect of various operations upon the brain on the secretory response to insulin hypoglycemia in gastric fistula dogs. They found that the response remains after decortication but after decerebration it disappears in most animals, although a few give a reduced, delayed response. This would suggest that the main site of action of the hypoglycemia in stimulating gastric secretion is in a part of the brain above the medulla and below the cortex, probably the hypothalamus.

The studies of Morton & Stavraky (32) and of Stavraky (33) promise to add important fundamental facts to our knowledge of the control of acid secretion. These workers injected acetylcholine directly into the arteries of the stomach and found that when only the fundic gland area received the acetylcholine an abundant alkaline secretion devoid of pepsin was produced. Histologic studies indicated that this secretion arose from the mucoid neck cells.

When histamine was injected intraarterially after acetylcholine had been given an acid secretion with high pepsin content was produced. High doses of acetylcholine inhibited the acid secretory response to histamine but no dose of acetylcholine could be found which would stimulate acid secretion with acting alone. This was confirmed by Uvnäs (34). These findings speak strongly against the theory that acetylcholine is the sole neurohumoral agent for the vagal stimulation of gastric acid secretion. Babkin's assumption (35) that acetylcholine causes histamine to be released in the gastric mucosa does not clarify the picture because intraarterial injection would be expected to be capable of causing this histamine release. Perhaps the suggestion of von Euler (36) that certain autonomic nerves are histaminergic is applicable here; perhaps both acetylcholine and histamine are released by the postganglionic vagal fibers. Since parasympathomimetic drugs are capable of stimulating acid secretion when they are given in appropriate doses subcutaneously, it must be assumed that they cause the release of some stimulating agent as an intermediate step. The possibility that they cause gastrin to be released from the pyloric mucosa suggests itself. On the other hand, the notion is not tenable that vagal impulses cause gastrin release, a proposal originally made by Uvnäs whose studies on this subject have recently been reviewed by Kahlson (37). It is well known that in a dog with a Heidenhain pouch when the main stomach is responding to sham feeding or insulin hypoglycemia the pouch fails to respond. If these vagal mechanisms were causing the release of gastrin, the Heidenhain pouch would be stimulated.

The effect of mecholyl in beeswax on gastric secretion in dogs was studied by Wener *et al.*, (38), who found that with this mode of administration there is a stimulatory phase followed by a marked inhibitory phase, again confirming the biphasic action of parasympathomimetic drugs. Uvnäs (34) was able to stimulate the secretion of gastric juice in anesthetized cats by subcutaneous injection of appropriate doses of physostigmine or diisopropylfluorophosphate.

In human subjects and in dogs the minimal rate of histamine administration necessary to stimulate gastric secretion has been determined [Hanson, Grossman & Ivy (39)]. The average values found were 0.004  $\mu\text{g. per kg. per min.}$  in man and 0.04 in the dog. In the dog the dose required to evoke maximal secretory rates

was 1.3  $\mu$ g. per kg. per min. and this produced 80 cc. of juice per hour containing 140 mM per l. of hydrochloric acid (average values). The effectiveness of a given dose of histamine was the same when it was given at frequent intervals subcutaneously or continuously intravenously, and vagotomized dogs exhibited no difference from intact dogs in regard to threshold for secretion or size of secretory response. (In view of the findings of Antia & Ivy, see below, it should be mentioned that these dogs had been vagotomized a year or more before the studies were made.)

A wetting agent which produces urticaria when injected intravenously in dogs has been found to cause stimulation of gastric secretion; both of these effects are abolished by Benadryl [Grossman & Robertson, (40)], although Benadryl does not depress the gastric secretory response to histamine.

Various commercial preparations of protein hydrolysate were injected intravenously in human subjects by Zweig, Meyer & Steigmann (41), who found that when these substances were given at a rapid rate stimulation of acid secretion occurred in 55 per cent of the tests. No effect on gastric motility was found. The stimulating effect of these products could be correlated to some extent with their histamine content. Crider & Walker (42) also investigated the effect of intravenous administration of a protein hydrolysate on gastric secretion. A woman with a gastric fistula was their only subject and they claim to have observed a depression of both secretion and motility.

Intravenous injection of theophylline preparations was found to stimulate gastric secretion in man according to Schlesinger *et al.* (43). Robertson & Ivy (44) found that the xanthine derivatives which stimulate gastric secretion in man, caffeine and theophylline, fail to stimulate when given alone in the dog but they are capable of potentiating the response to histamine in this species.

Schachter (45) showed that chloralose, urethane, pentothal, and occasionally pentobarbital stimulate gastric secretion in gastric fistula dogs. He believes that this stimulation usually does not occur in acute experiments because the trauma to the stomach prevents the response. Kaulbersz & Bilski (46) confirmed the stimulatory action of bile on gastric secretion.

*Inhibition of gastric secretion.*—Logan (47) states that spontaneous or experimentally induced acidosis did not detectably inhibit gastric acid secretion in dogs or men. The inhibitory effect

of sucrose on the secretion of acid in response to a gruel fractional test meal was studied in human subjects by Hunt & Spurrell (48).

Biological extracts capable of inhibiting acid secretion continue to hold some interest. It is welcome to see that attention is being given to improvement of the accuracy of methods of assaying gastric secretory inhibitors, because progress in the purification of these substances cannot be made unless good quantitative measurements of potency are possible [Code *et al.* (49), Blickenstaff & Grossman (50)]. A carefully standardized two dose histamine test in anesthetized cats proved suitable for measuring the inhibitory action of enterogastrone and urogastrone preparations in the hands of Howat & Schofield (51). This is in contrast to the report of Uvnäs (52), who claimed that enterogastrone did not inhibit histamine stimulated secretion in the cat; he probably did not have active preparations. Results of assays of enterogastrone and urogastrone carried out in rats with pyloric ligature showed poor correlation with those performed on dogs with gastric pouches [Visscher & Grossman (53)].

Sandweiss and his associates (54 to 57) have continued their studies upon the effect of extirpating various endocrine glands upon the output of urogastrone in the urine. They have confirmed their earlier observation that urine extracts from hypophysectomized dogs do not produce the characteristic inhibition of gastric secretion seen with extracts from normal dogs. Oophorectomy also appeared to cause the disappearance of urogastrone from the urine whereas thyroidectomy had no effect.

Gershbein and co-workers (58) stated that *n*-butyl alcohol fractionates enterogastrone preparations into an extract which inhibits and a residue which stimulates gastric secretion.

Reports of several additional studies on the effect of enterogastrone on gastric secretion in man have appeared. When a commercially available enterogastrone preparation was given in doses up to 400 mg. intramuscularly by Ferayorni, Code & Morlock (59), the secretion of acid in response to histamine or an Ewald test meal was not inhibited in their human subjects. Kirsner, Levin & Palmer (60) used the dialysate of this same commercial enterogastrone preparation and found that it was necessary to give 5 gm. of the material intramuscularly in order to depress significantly the nocturnal secretion of acid in ulcer patients (in evaluating these results one should remember that intramuscularly

enterogastrone is only one-fifth to one-tenth as effective as intravenously). These same workers (61) demonstrated that the injection of a nonspecific protein (sterile lactalbumin) did not cause a similar depression of secretion even in those cases in which a febrile reaction occurred. Oral administration of a pregnant mare's urine extract in 7.5 gm. doses also failed to depress secretion (62).

Code and his co-workers (63, 64) have confirmed the work of Brunschwig which showed that the intravenous injection of alcoholic precipitates of gastric juice inhibits gastric secretion. Commercial gastric mucin was also found to be effective, and this fact is of some importance because it indicates that inhibitory substances can be extracted from the gastric, as well as the intestinal, mucosa. This raises the important question of whether the so-called enterogastrone extracts owe their activity to such mucinous substances rather than the true hormone.

The intravenous injection of a purified histaminase prepared from hog kidney depressed the gastric secretory response whether it was evoked by histamine or by food or other drugs [Grossman & Robertson (65)]. Whether the inhibition was due to the histaminase or to some other constituent of the extract could not be decided.

The drug tetraethylammonium received considerable attention in the literature of the past year. Neligh & co-workers (66) state that complete cessation of motility of the stomach and intestine occurs for a short period following the intravenous injection of tetraethylammonium chloride in human subjects examined radiologically. They also found that the basal gastric secretion of acid was reduced and the secretory response to hypoglycemia was prevented. The drug caused a 70 per cent reduction in the secretory response to histamine administered continuously intravenously in the studies of Zweig and associates (67) on human subjects. In dogs Robertson & Grossman (68) found that tetraethylammonium had no effect on histamine-induced secretion but counteracted the secretory response to sham feeding. In patients with peptic ulcer Cayer and co-workers (69) found that 600 mg. of the drug given intramuscularly had only a slight inhibitory effect upon the basal secretion, and Ferrer (70) states that 20 mg. per kg. intramuscularly every 4 hrs. was required to produce a consistent and significant depression in nocturnal secretion.

The antihistaminic drug Thephorin is stated by Lehmann &

Stefko (71) to be capable of inhibiting the gastric secretory response to histamine in Heidenhain pouch dogs. This is in contrast to other antihistaminics which are ineffective in counteracting the gastric secretory stimulation produced by histamine, a fact again confirmed by the work of Gilg in humans (72). The administration of 15 gm. of urea orally reduced the concentration of acid in the gastric juice secreted in response to histamine in human subjects (73).

*Pepsin.*—Uvnäs (74) has reinvestigated the old theory of Sawitsch concerning the existence of a pyloric mechanism for the control of pepsin secretion. He claims that the injection of extracts of pyloric mucosa or distention of the pyloric part of the stomach stimulates pepsin secretion; his data in support of these claims are meager. Hunt (75) believes he has demonstrated a peptic synergist in gastric juice. He used plasma protein as a substrate and it is probable that the discrepancies between his findings and those of Bucher *et al.* (76) are due to the use of this substrate.

The excellent studies of Mirsky and co-workers (77, 78, 79) on uropepsin excretion have clarified a number of points. They have demonstrated for the first time that the intravenous injection of pepsinogen in a dog results in an increase in uropepsin excretion, whereas feeding or injecting pepsin has no such effect. This supports the notion that pepsinogen is secreted in an "endocrine" fashion directly from the chief cells into the blood stream. The rate of uropepsin excretion was found to be fairly constant from hour to hour and from day to day, being unaffected by composition of the urine, eating, or activity. The average rate of uropepsin excretion in ulcer patients was distinctly higher than in normal subjects. Bucher & Anderson (80) measured the uropepsin output in cats treated with caffeine and histamine and were unable to find clear cut evidence for an increase. Bucher (81) reopened the question of the effect of histamine on pepsin secretion and produced evidence in support of her former conclusion that when gastric secretion is maintained by histamine, after the initial washing out of pepsin, the pepsin concentration of the juice falls to low levels but never to zero.

*Mucus.*—Important advances are being made in our understanding of the nature of the constituents of the mucus of the stomach and the mechanisms that control its secretion. Glass & Boyd (82) describe three main components, namely, dissolved

mucoproteose, dissolved mucoprotein from the neck mucoid cells, and mucoid of the visible gastric mucus from the surface epithelial cells. Grossberg, Komarov & Shay (83) determined the glucuronic acid and glucosamine contents of gastric juice after various stimuli. They devised a method of calculating the concentration of neutral and acid polysaccharide from the values of these determinations.

Hollander & Kraus (84) found that the topical application of magnesium or calcium salts did not prevent the desquamation of gastric mucus membrane induced by eugenol.

*Other aspects of gastric secretion.*—Crider & Walker (85) studied the effect of various emotional states upon the motor and secretory activity of the stomach in a woman with a gastric fistula. Since they found that anger, resentment, fear, and anxiety all produced depression of gastric activity, they believe the difference between their results and those of Wolf & Wolff on their male subject were due to sex differences. Obviously this conclusion is unwarranted on the basis of the study of a single case in each sex.

After 90 per cent of the vessels of the stomach are ligated, Holm and co-workers (86) found that on histologic examination some disappearance of parietal and chief cells in the superficial one-third of the mucosa occurs. Mercuric chloride applied to the gastric mucosa produced marked desquamation of the surface epithelium and suppression of acid secretion [Dreyer & Leonard (87)].

#### VAGOTOMY

In the dog Antia & Ivy (226) found that bilateral vagotomy caused a reduction in the secretory response both to histamine and to urecholine. The emptying of a liquid meal from the stomach was unimpaired and the delay in emptying produced by fat was unaffected by vagotomy. In patients treated for peptic ulcer by vagotomy, Stein & Meyer (88) found the secretory response to histamine and to caffeine to be markedly reduced. The cause of the reduced response to histamine which occurs after vagotomy is not known but may be related to the ability of acetylcholine to potentiate the acid secretory response to other stimuli.

Hollander (89) set forth the standards for the performance and interpretation of the insulin test. Gullickson & Campbell (90) proposed that the gastric excretion of neutral red be used as a criterion of completeness of vagotomy.

Postlethwait and co-workers (91) observed the effects of vagotomy on gastric motility in rabbits, dogs, and human subjects. In rabbits vagotomy caused cessation of motility for 12 to 48 hr. followed by hypermotility with gastric retention. It is interesting to speculate on whether the hypermotility seen in the rabbit after vagotomy is related to the marked tendency of rabbits to develop gastric ulcer after vagotomy. In human subjects the basal intra-gastric pressure was found not to be reduced after vagotomy although gastric contractions were much depressed, confirming a similar observation by Quigley, who used more delicate methods for measurement of pressure.

The gastric retention associated with absent or diminished antral peristalsis can, according to Machella & Lorber (92), be largely relieved by the administration of the parasympathomimetic drug Urecholine. Stein & Meyer (93) using the balloon and kymograph method could detect no contractions of the fundic part of the stomach for periods extending up to 27 months after vagotomy. Doryl and Urecholine caused strong contractions whereas prostigmine and mecholyl had little or no effect on gastric motility in these patients after vagotomy.

Thomas & Komarov (94) present the opinion that vagotomy as usually performed in man and animals is seldom complete (even when the insulin test is negative) and that complete vagotomy leads to impairment of digestion incompatible with life. The authors support this point of view mainly with the observations made by Pavlov and his co-workers many years ago. Actually there is no good evidence in support of this opinion, all the evidence being to the contrary.

#### PEPTIC ULCERS: EXPERIMENTAL ASPECTS

The literature on experimental production and treatment of peptic ulcer has recently been reviewed by Berg (95). Saltzstein and his co-workers (96) have summarized their results in the treatment of 374 Mann-Williamson dogs. The experimental and clinical evidence bearing on the relationship of bone trauma to the development of acute gastroduodenal lesions has been reviewed by Friesen and his associates (97).

Wang & Grossman (98) showed that the addition of lysozyme to acid and pepsin enhanced its ulcerogenic action when perfused into the stomach of rats. Wener and co-workers (99) produced a

few gastric and duodenal ulcers in dogs by the prolonged administration of large doses of mecholyl, but most of the lesions were hemorrhagic erosions.

The histamine-induced ulcer continues to be widely used. Hanson, Grossman & Ivy (100) injected histamine solutions into dogs continuously by the subcutaneous or intravenous route and found that approximately 1  $\mu$ g. per kg. per min. of histamine base was required to produce ulceration consistently within 15 days. McCorrison and co-workers (101) confirmed the fact that rabbits do not get ulcers when given histamine in beeswax but, when nitroglycerine in beeswax is also given, ulcers occur in about 40 per cent of the animals. Lillehei & Wangensteen (102) reported that removal of the celiac ganglion plus stripping of the nervous plexuses along the arteries greatly increases the susceptibility of dogs to the histamine-induced ulcer. These authors made the important observation that the discrepancies in the literature on the effect of celiac ganglionectomy on gastric function were probably due to the fact that ganglion cells are present along the arteries and these must be removed in order to get a complete denervation. Trabucchi (103) confirmed the finding that the simultaneous administration of antihistaminic drugs with histamine permits doses of histamine to be given which are so large that ulcer may occur within a few hours. Poth and associates (104) found that ligation of the pancreatic duct or pancreatectomy increased the rate of formation and the severity of ulcers produced by histamine in beeswax in dogs whereas alloxan diabetes had no influence. Hale & Grossman (105) found that surgically produced excision ulcers of the stomach healed within 3 weeks and the scar did not break down when histamine in beeswax was given even though ulcers did form in immediately adjacent areas.

In order to determine how much acid is required to produce ulcers in dogs when this factor is operating alone, Fogelman, Grossman & Ivy (106) continuously infused acid-pepsin solutions into the stomachs of dogs through a gastrostomy. Ten cc. per kg. per hr. of 0.15 *N* HCl with pepsin was required to produce ulceration when acidosis was prevented by simultaneous intravenous administration of a suitable amount of sodium bicarbonate solution. This volume and concentration of acid is about equal to the maximal secretory capacity of the stomach.

Several interesting studies on the rumenal ulcers of the rat with

pyloric ligation have appeared. Shay and his co-workers (107) reported that the prefeeding of protein hydrolysates partially protected against these lesions without altering gastric secretion. The study of McGinty and his associates (108) showed that purified bacterial pyrogens reduced the acidity and prevented ulcers in Shay rats. This is an important observation because it raises the question of whether those urinary and intestinal extracts which have been shown to be effective in preventing these ulcers may not owe their activity to their pyrogen content.

Holm & Mackay (109) ligated all of the arteries of the lesser curvature and 90 per cent of those of the greater curvature in Mann-Williamson dogs and reported that the occurrence of ulcers was delayed but not prevented by this procedure. The Mann-Williamson dogs of Visscher & Lyster (110) which received an enterogastrone concentrate did not have a significantly lower incidence of ulcer than the untreated controls. This failure to confirm the results of Ivy and his co-workers could well be due to the use of inactive extracts.

The possible relationship between the choleresis produced by cinchophen and the occurrence of ulcers when this drug is fed was studied by Magee and co-workers (111). Choleresis was marked in the guinea pig, slight in the cat, and absent in rabbits and rats; ulcers occurred consistently only in the cat. In dogs with isolated pouches of the first portion of the duodenum, Hartiala & Grossman (112) showed that the feeding of cinchophen markedly reduced the volume and alkalinity of the secretion.

Subtotal gastric resection with pyloric exclusion or with pyloric excision was performed in dogs by Schilling & Pearse (113). After recovery from the operation, all of the animals received histamine in oil and wax. The incidence of ulcer in the animals with pyloric exclusion was higher than in those with pyloric excision. If this difference is a true one and not due to sampling errors, it is difficult to explain how removal of the pyloric mucosa apparently alters the gastric secretory response to histamine.

The esophageal mucosa is highly sensitive to the destructive action of acid pepsin according to the observations of Wangenstein & Sanchez (114). Sanchez-Palomera & Wangenstein (115) described the production by irritants of erosions of the gastric mucosa. They did not describe the participation of migration of mucoid and parietal cells from the adjacent intact glands in the

repair process, a phenomenon which has been carefully studied and well described by Grant (116).

Levin and his co-workers have written several more papers extending their observations on the fasting nocturnal gastric secretion in normal persons and in ulcer patients. Marked variation from person to person, and from hour to hour or from day to day in the same person, was encountered (117). Despite these variations, certain patterns and differences were discernible. The volume and output of hydrochloric acid were significantly higher in the majority of cases during the first 6 hr. of the night than during the last 6 hr. The average output of free hydrochloric acid in ulcer patients was found to be three times as high as in normal persons (118). In patients studied both during an exacerbation and after healing had taken place, no difference in acid output was observed (119). A few ulcer patients secreted as much as eight times the amount of acid that an average normal individual secretes, values as high as 5,000 mg. of hydrochloric acid per 12 hr. being observed (120). In a provocative report from the same clinic Ricketts and associates (121) describe the results with the use of x-ray irradiation of the gastric fundus in the treatment of peptic ulcer. Histamine-refractory achlorhydria, lasting for periods varying from days to years, was achieved in a significant percentage of cases. Winkelstein & Hess (122) claim that the secretory response of the duodenal ulcer patient to insulin is characterized by an increased acid concentration whereas the response to histamine shows only increased volume, a claim not fully in accord with the previous reports of other workers.

#### BILE SECRETION

Annegers & Friend (123) made the important observation that cholic acid output in dogs with cholecystonephrostomy increases linearly as the casein in the diet increases, but this effect could not be attributed to amino acids because casein hydrolysate did not produce it.

Cantarow and his co-workers (124) have made valuable studies on the quantitative aspects of bilirubin and bromsulfalein excretion in bile in dogs provided with the Thomas type metal cannula in the duodenum which permits direct cannulation of the common bile duct during the period when observations are being made. They found that a dose of 1 mg. per kg. of bilirubin was excreted

within 3 hr., mainly by a rise in concentration of the pigment in the bile without much change in volume rate. Bromsulfalein was handled much like bilirubin and it did not interfere with endogenous bilirubin excretion. When bilirubin and bromsulfalein were given together bromsulfalein was excreted as efficiently as when it was given alone, but the excretion of bilirubin was depressed.

Grossman *et al.* (125) demonstrated that purified secretin stimulated the volume rate of bile flow in human subjects with T tubes in the common bile duct. Cholic acid and bilirubin output were not increased, indicating that secretin induces a hydrocholesis similar to that produced by dehydrocholic acid. When serum of dogs with ligated common bile duct containing alkaline phosphatase in high concentration is transfused into normal dogs, the output of alkaline phosphatase in the bile and pancreatic juice is not increased [Wang & Grossman (126)]. This speaks against the theory that the rise of alkaline phosphatase which occurs in liver disease is due to damming back of serum phosphatase normally excreted by the liver.

Freeman (127) has described a clamp which facilitates the performance of portocaval anastomoses in dogs.

#### PANCREAS

The literature on tests of pancreatic function has been reviewed by Popper & Necheles (128). Thomas (129) has summarized his views on the functional innervation of the pancreas. He believes that local nervous connections between the duodenum and the pancreas are responsible for the high concentration of enzymes found in the juice secreted in response to the presence of peptones or soaps in the duodenum. He rejects the possibility that pancreozymin may be released by these substances because atropine is known to have no effect upon the action of pancreozymin whereas it markedly depresses the enzymic response to the substances which act in the duodenum. The possibility that atropine may prevent the release of pancreozymin, even though it cannot prevent its action once released, must be considered.

Meyer and co-workers (130) have succeeded in crystallizing human pancreatic amylase. They found it to be indistinguishable from human salivary amylase but different from hog amylase which has a lower specific activity. Lane & Williams (131) have made the interesting suggestion that inositol is a constituent of the molecule of pancreatic amylase.

Modern principles of bioassay have been applied to the assay of secretin and pancreozymin by Burn & Holton (132) and to secretin and cholecystokinin assay by Greshbein and co-workers (133). These methods call for the use of reference standards and efforts to make these available to all who are engaged in work in this field will determine the usefulness of the methods.

Wang, Grossman & Ivy (134) showed that in anesthetized dogs increasing the rate of secretin administration increased the rate of flow of pancreatic juice without increasing the minute output of amylase. Pancreozymin increased the concentration of amylase but did not influence the rate of flow or the concentration of alkaline phosphatase. This constitutes the first clear demonstration that pure secretin does not stimulate enzyme output.

Waldron & Thomas (135) present evidence suggesting that mechanical stimulation of the duodenum is capable of inciting the flow of pancreatic juice. Routley and co-workers (136) are making extensive studies on the effect of drugs and meals on pancreatic secretion in dogs with total external fistulas.

According to Friedman & Snape (137) the production of insulin hypoglycemia simultaneously with the administration of secretin results in an elevation in enzyme concentration but no increase in volume as compared with secretin alone.

Several excellent clinical studies on the use of the secretin test in the diagnosis of pancreatic disease have appeared [Dreiling & Hollander (138), Dornberger *et al.* (139)]. It is of interest to note that as pancreatic disease progresses impairment of volume and bicarbonate secretion are seen before depression of enzymes occurs.

Knight and co-workers (140) found that injection of prostigmine does not cause a rise in the level of serum diastase in normal individuals but it does so in some cases of pancreatic disease.

Baggenstoss and associates (141) were able to extract secretin from the intestines of human post mortem material. In the one case of fibrocystic disease of the pancreas studied by them, no secretin was found in the extract. Speculation about the significance of this finding should be reserved until it is confirmed or disproven.

Nothman and co-workers (142) confirmed the observation that ligation of the pancreatic duct in dogs leads to a rise in serum lipase concentration which can be caused to return to normal by pancreatectomy. Lium & Maddock (143) confirmed earlier workers who had shown that ligation of the pancreatic ducts had to be

accompanied by stimulation of pancreatic secretion by food or drugs in order to produce edema of the gland. The studies of Popper and his associates (144) extended this finding to show that the addition of circulatory impairment to ligation of the duct and stimulation of secretion led to necrosis and hemorrhage of the pancreas. The importance of stimulation of pancreatic secretion in the pathogenesis of pancreatic disease was also demonstrated in the experiments of Popper (145), who showed that transection of the pancreatic duct was followed by plugging with omentum and fibrosis if the animal was starved but led to fat necrosis if the animal was fed.

The uptake of radioactively tagged methionine was found by Wheeler and co-workers (146) to be much reduced in the pancreas made atrophic by duct ligation. By a correlated histochemical and physiological study Wang, Wang & Ivy (147) followed the course of degeneration of the pancreas after duct ligation in rabbits.

#### GASTROINTESTINAL MOTILITY

Several new devices for recording gastrointestinal motor activity have been described [Steggerda & Clark (148, 149), Posey *et al.* (150)]. Although these methods employ new principles such as electrical recording and photokymography, there is a question as to whether they accurately measure intraluminal pressures [Quigley, (151)].

Hwang, Grossman & Ivy (152) have found that the motor nerve supply of the cervical portion of the esophagus in the dog, cat, rabbit, monkey, guinea pig, and rat is derived from two widely separate vagal branches. In the dog and cat the main motor innervation is the pharyngoesophageal nerve, which arises above the ganglion nodosum.

A wide interest continues to be shown in the study of antispasmodics, a clear indication that an ideal drug for clinical use is not yet available [Child & Woodbury (153), Craver *et al.* (154)]. Posey and co-workers (150) made detailed studies on ileostomy and colostomy patients. They concluded that with the exception of atropine, none of the common antispasmodics depress motility when given orally in their usual doses.

Lorber & Machella (155) performed a careful study of Syntropan and found that it produced significant inhibition of gastro-

intestinal motility only when given intravenously and by this route undesirable side effects were noted. The experiments of Higgins and co-workers (156) showed that atropine was more effective in inhibiting gastric motility when given intravenously whereas the synthetic antispasmodics which they studied were more effective when given intragastrically. This suggests that some of the antispasmodic action of these synthetic drugs may be due to their local anesthetic properties, a notion which has caused several investigators to study the action of local anesthetics on the activity of the intestinal muscle *in vitro* [Child (157)]. Feldberg & Lin (158) found that local anesthetics and curare-like drugs when added to the bath containing isolated rabbit ileum inhibit the peristaltic (circular) but not the shortening (longitudinal) response to distention.

Tetraethylammonium was found by Dodds and co-workers (159) to cause marked depression of gastric emptying when given in a dose of 0.5 gm. intravenously to human subjects. In distinct contrast, Lane, Robertson & Grossman (160) found this drug to have little effect on gastric emptying in dogs given 10 mg. per kg. intravenously. However, Longino, Chittum & Grimson (161) using a more potent ganglionic blocking agent, 2,6-dimethyl diethyl piperidinium bromide, observed distinct delay in gastric emptying in dogs given 5 or 10 mg. per kg. intravenously.

The tone and contractions of Thiry-Villa intestinal loops in unanesthetized dogs was found to be depressed by cycloheptenyl-ethyl barbituric acid as well as by other barbiturates in the studies of Halbeisen and co-workers (162).

Using the ingenious pyloric inductograph in intact unanesthetized dogs, Louckes, Brady & Quigley (163) found that the intravenous injection of 0.5 to 4  $\mu$ g. per kg. of epinephrine abolished motility for from 30 to 80 sec. At the same time an increase in sphincter tone occurred.

Lorber, Komarov & Shay (164) have studied the effect of sham feeding on the gastric motor activity of the dog. Hightower and associates (165) investigated the effect of prostigmine and Urecholine on human gastric motility.

Stickney, Northup & Van Liere (166) found that when the carbon dioxide content of inspired air is varied between 6 and 12 per cent, an increase in emptying time of the stomach of dogs takes place which is proportional to the elevation in carbon dioxide

level. Therapeutic doses of chloral hydrate, bromural, pentobarbital, and paraldehyde result in acceleration of gastric emptying in dogs (167). It is of interest to recall, as noted elsewhere in this review, that these drugs inhibit intestinal motility and stimulate gastric secretion.

In ileostomy and colostomy patients Posey, Brown & Bargaen (168) found the tone and motility depressed or abolished for an average of 40 min. after an intravenous injection of a dose of tetraethylammonium chloride averaging 260 mg. From this it would appear that the intestine is more sensitive than the stomach to the action of this drug.

Douglas (169) exteriorized the duodenum of dogs without interrupting its continuity. He found the loop usually to be quiescent during fasting. From 50 to 140 sec. after feeding activity began consisting of waves with a frequency of 17 to 19 contractions per min. The response of the duodenum to morphine has been studied by Loomis (170) in anesthetized dogs. He noted tachyphylaxis to the action of morphine which consisted of an increase in tone and contractions of the circular muscle with an opposite effect upon the longitudinal component.

Krueger (171) has extended his studies on the quiescence which precedes peristaltic contractions in the ileum and states that both tone and rhythmic contractions are involved.

Whitrock and co-workers (172), studying the effect of extrinsic denervation on the intestine, have confirmed the fact that the intestino-intestinal inhibitory reflex is carried by way of the sympathetic nerves exclusively.

When intestinal loops are spatially transposed by surgical procedures in dogs, the time of onset of contractions after feeding is altered but the rate of contractions is not [Watkins & Mann (173)]. This adds further evidence to the notion that the initiation of contractions is due to local stimulation by the presence of material in the lumen. This same idea is also supported by results of the studies of Faik, Mann & Grindlay (174) on intestinal motility in vagotomized dogs. In these animals the onset of activity after feeding was delayed, presumably due to the delay in gastric emptying.

Craver and co-workers (175, 176) have studied the motor response of Thiry-Villa loops in anesthetized dogs. They found that antihistaminics and atropine are both capable of annulling spasm induced by intravenous injection of histamine. Tetraethylam-

monium and the anticholinesterases physostigmine, prostigmine, and diisopropylfluorophosphate potentiated the response to histamine but mecholyl and doryl did not. These findings are considered as supporting the theory of Ambache (177) that histamine acts on smooth muscle by releasing acetylcholine; however, Feldberg (178), has pointed out that another interpretation of such facts is possible. Because they found that antihistaminics counteract the purgative action of drastic cathartics in rats and cats, Erspamer & Paolini (179) suggest that these substances owe their action to the release of histamine.

In normal human subjects studied by means of proctoscopy and balloon and kymograph, Almy and co-workers (180) were able to cause a marked increase in the contractile state of the sigmoid colon in 50 per cent of the subjects by such diverse stimuli as cold pain, compression of the head, hypoglycemia, or discussion of emotionally charged topics. According to the authors the effect was seen only when the stimulus was regarded as a threat to security. Patients with spastic constipation showed the same type of reaction (181) but it occurred in all subjects; the authors concluded that colonic behavior is normal in these persons but susceptibility to stress is heightened.

Gaston (182) studied human patients by manometric methods and showed that the tone of the external sphincter of the anus is not continuous but is phasic and is co-ordinated with the activity of the rectum by way of a reflex. This reflex can be interrupted, with ensuing fecal incontinence, by cord transection, by injury to the efferent nerves, or by removal of the afferent limb as a result of resection of the entire rectum.

The isolated intestinal muscle strip, an old tool in physiology, is playing a new role in the unraveling of the biochemistry of metabolic activities. By the study of the effect of enzyme inhibitors and of products of intermediary metabolism on the activity of such strips, important knowledge about metabolic processes is being gained. Thus far only preliminary reports of these studies have appeared [Weeks & Chenoweth (183), Farah *et al.* (184), Ewing *et al.* (185)].

Using isolated intestine loops from dogs Bean & Mohamed (186, 187) have studied the effect of arterial pressure on blood flow and intestinal motility and conversely the effect of motility upon blood flow.

Collins (188) reports that in the isolated guinea pig ileum

tetraethylammonium alone causes contraction, together with histamine or angiotonin it augments the response whereas it depresses the response to barium or acetylcholine.

#### ABSORPTION

With the recognition that enzymic processes participate in many mechanisms that were formerly vaguely designated as "selective absorption," renewed interest in problems of gastrointestinal absorption can be anticipated. However, at present the field is not a highly active one.

The effect of deficiencies or excesses of certain hormones or vitamins on intestinal absorption has been studied by Althausen (189) and a number of valuable facts have been established. Feeding thyroid extract to rats was found to lead to an increase in the rate of absorption of glucose, galactose, and oleic acid but not of xylose or alanine. Phlorizin was found to depress the absorption of those substances which thyroid stimulates. To show that the absorption of glucose from the kidney tubules was analogous to that in the intestine, Althausen was able to demonstrate that feeding thyroid caused an increase in the capacity of the kidney to reabsorb glucose from the glomerular filtrate. Vitamin B complex deficiency led to a decrease in the rate of absorption of glucose and galactose, whereas during recovery from the deficiency a supernormal rate of absorption of these substances occurred. A number of these findings have been applied to clinical cases of hormone and vitamin imbalance.

Heersma & Annegers (190) demonstrated the interesting fact that cholecystectomy in the dog has no effect upon fecal fat or nitrogen excretion indicating that gall bladder function is not required for normal absorption.

Regeneration of the intestinal lacteals is so rapid that within about one week after resection of the mesenteric lymph nodes in dogs no abnormality of the alimentary lipemia curve or of fecal fat excretion could be detected [Clarke, Ivy & Goodman (191)].

When Vitamin A is dispersed in an aqueous medium the rate of absorption is found to be much higher than when it is dissolved in oil, the difference is especially striking under conditions of impaired absorption [Popper & Volk (193), Popper, Steigmann & Dyniewicz (192), Danielson *et al.* (227)].

Karel & Fleischer (194) studied the absorption of ethyl alcohol

from the stomach of the rat and concluded that hydrostatic pressure was a factor in determining rate of absorption. Karel (195) reviewed the literature on gastric absorption.

Robinson and associates (196) reported on the chemical changes occurring in isotonic saline solutions placed in successively lower levels of the human small intestine. Bucher and co-workers (197) studied the changes in sodium sulfate solutions placed in loops of small intestines of dogs.

Althausen and co-workers (198) made careful studies of absorption and digestion in a patient in whom all of the small intestine except the duodenum and 15 cm. of jejunum had been resected.

#### MISCELLANEOUS

Thomas (199) has written on the subject of recent advances in gastrointestinal physiology. Uvnäs (200) showed that dibenamine was capable of blocking the secretory impulses to the submaxillary gland produced by stimulation of the sympathetic trunk in the cat.

The study of Barclay & Bentley (201) on the vascularization of the human stomach may well become a classic in this field. By microradiography after injection of opaque media into the vessels of human stomachs removed at surgery or autopsy, they obtained evidence suggesting that an arteriovenous anastomosis exists in the region of the submucous plexus. Opening of these shunts puts a stop to active circulation through the small vessels of the mucous membrane.

Intragastric temperatures as high as 56°C. were recorded in human subjects eating mush at 83°C. [Davis & Ivy (228)].

In the fetal rat with the placental circulation intact starch or milk placed in the stomach becomes digested [Hartmann & Wells (202)]. Hare & Stewart (203) observed the development of spontaneous adenomatous gastritis in mice of the dba strain. Phillipson (204) has described a method of measuring the flow of digesta from the stomach of sheep, and McDonald (205) has measured the extent of conversion of food protein to microbial protein in the rumen of sheep. Jefferson and co-workers (206) studied the effect of various gastric operations on the oral glucose tolerance test in dogs. Grant, Grossman & Ivy (207) found that the addition of bile or bile salts to opaque gastric mucus resulted in cytolysis of the

cells suspended in the mucus with a concomitant decrease in the opacity of the mucus. Miller and co-workers (208) studied the resistance of a flap of gastric mucosa explanted onto the abdominal wall to various chemical and physical agents.

Blickenstaff & Grossman (209) found that all the simple food-stuffs, carbohydrate, fat, and protein, were capable of stimulating the secretion of mucus from an isolated pouch of the first portion of the duodenum in the dog.

In human subjects Wolf (210) found that nauseants such as ipecac or cupric sulfate did not exert an effect when confined to the stomach but acted quickly when they entered the duodenum.

Borison (211) and Borison & Wang (212) succeeded in localizing the area of the medulla concerned in vomiting in the cat. Electrical stimulation of the tractus solitarius, gustatory nucleus, and a small portion of the reticular formation elicited vomiting whereas lesions in the dorsolateral portion of the reticular formation impaired the emetic response to apomorphine.

Lasichak & Levey (213) administered glutamic acid into the portal circulation of dogs and found that a more rapid rate of infusion was required to produce vomiting than when the amino acid was given into an extremity vein.

The incidence of abdominal adhesions following the placing of talcum powder in the peritoneal cavity of dogs was found to be significantly lower when the animals were fed promptly and given prostigmine than when starved and given atropine [Schiff *et al.* (214)]. Nemir and co-workers (215) were able to keep dogs with simple intestinal obstruction alive as long as 45 days by parenteral fluid and nutrient therapy.

The intraperitoneal pressure in human subjects was found to average 8 cm. of water in supine subjects and 20 cm. of water in erect subjects [Drye (216)].

Lack of roughage in the diet, state Carlson & Hoelzel (217), leads to diverticulosis of the colon in old rats. Psyllium seed husks prevented these diverticuli.

The study of Kirk (218) on the quantity and composition of human colonic flatus revealed that on the average 1.47 ml. per min. can be withdrawn from the colons of normal subjects. Feeding of Brussel sprouts produced a large increase, whereas lactose and cow's milk caused no change. Patients with colonic dysfunction did not show excessive gas excretion. Poggrund & Steggerda (219)

introduced air, nitrogen, and carbon dioxide into the colon of human subjects and measured the rate of absorption of these gases. The rate of absorption was found to be well correlated with the partial pressure gradient between bowel lumen and venous blood.

The *Salmonella* organism which causes ulcerative cecitis in rats was found by Bloomfield & Lew (220) to be sensitive to streptomycin. The concentration of lysozyme in the stools of human subjects was studied by Grace and co-workers (221). The normal range of 0.3 to 1.7 units per gm. was greatly exceeded by patients with ulcerative colitis who may show values as high as 100 units per gm. The occurrence of high values is associated with exacerbations of the disease, and the investigators feel that certain life situations which are interpreted by the patient as a threat to security are associated with these flare-ups. Wener, Hoff & Simon (222) administered mecholyl in large doses over long periods to dogs and noted hyperemia, hemorrhage, erosions, and acute ulcers in the colon which they felt were similar to the lesions found in ulcerative colitis.

An interesting attempt to measure the thermal conductance of the colonic wall as a possible index of blood flow has been made by Scarborough and co-workers (223). An experimental study in animals of the relationship of chemical structure to biliary concentrations in cholecystography was reported by Hoppe & Archer (224). Snape, Friedman & Swenson (225) employed the secretin test as a diagnostic aid in gall bladder disease. The basis of the test is that the choleric action of secretin causes an increased flow of bile into the intestine when because of disease the gall-bladder is unable to take up the bile.

#### LITERATURE CITED

1. JANOWITZ, H. D., AND GROSSMAN, M. I., *Hunger and Appetite—Some Definitions and Concepts* (Dept. Clinical Science, Univ. Illinois Coll. Med., 1949)
2. SANGSTER, W., GROSSMAN, M. I., AND IVY, A. C., *J. Applied Physiol.*, **1**, 637-42 (1949)
3. SANGSTER, W., GROSSMAN, M. I., AND IVY, A. C., *Am. J. Physiol.*, **153**, 259-63 (1948)
4. GROSSMAN, M. I., AND STEIN, I. F., *J. Applied Physiol.*, **1**, 263-69 (1948)
5. GOETZL, F. R., GOLDSCHMIDT, M., WHEELER, P., AND STONE, F. *Gastroenterology*, **12**, 252-57 (1949)
6. GOLDSCHMIDT, M., RAIMONDI, P. J., AND GOETZL, F. R., *Am. J. Physiol.*, **155**, 439 (1948)

7. JANOWITZ, H. D., AND IVY, A. C., *J. Applied Physiol.*, **1**, 643-45 (1949)
8. JANOWITZ, H. D., AND GROSSMAN, M. I., *Am. J. Physiol.*, **155**, 28-32 (1948)
9. JANOWITZ, H. D., HANSON, M. E., AND GROSSMAN, M. I., *Am. J. Physiol.*, **156**, 87-91 (1949)
10. JANOWITZ, H. D., AND GROSSMAN, M. I., *Federation Proc.*, **8**, 81 (1949)
11. ARCHDEACON, J. W., AND ALLEN, R. S., *Am. J. Physiol.*, **153**, 27-30 (1948)
12. TOWBIN, E. J., *Federation Proc.*, **8**, 158 (1949)
13. CIZEK, L. J., AND GREGERSEN, M. I., *Federation Proc.*, **8**, 25 (1949)
14. EDWARDS, L. E., AND EDWARDS, C. T., *Federation Proc.*, **8**, 40 (1949)
15. EDWARDS, C. T., AND EDWARDS, L. E., *Federation Proc.*, **8**, 39-40 (1949)
16. COY, F. E., JR., AND REHM, W. S., *Am. J. Physiol.*, **155**, 431 (1948)
17. DAVIES, R. E., *Biochem. J.*, **42**, 609-21 (1948)
18. BULL, H., AND GRAY, J. S., *Gastroenterology*, **4**, 175-82 (1945)
19. CONWAY, E. J., FITZGERALD, O., AND WALLS, D., *Nature*, **156**, 477-78 (1945)
20. DAVIES, R. E., AND LONGMUIR, N. M., *Biochem. J.*, **42**, 621-27 (1948)
21. CRANE, E. E., DAVIES, R. E., AND LONGMUIR, N. M., *Biochem. J.*, **43**, 336-42 (1948)
22. CRANE, E. E., DAVIES, R. E., AND LONGMUIR, N. M., *Biochem. J.*, **43**, 321-36 (1948)
23. REHM, W. S., AND HOKIN, L. E., *Am. J. Physiol.*, **154**, 148-62 (1948)
24. PATTERSON, W. B., AND STETTEN, De W., JR., *Science*, **109**, 256-58 (1949)
25. DAVENPORT, H. W., AND JENSEN, V., *Gastroenterology*, **11**, 227-39 (1948)
26. DAVENPORT, H. W., AND JENSEN, V., *Gastroenterology*, **12**, 630-36 (1949)
27. SHELDON, M., AND GROSSMAN, M. I., *Am. J. Physiol.*, **155**, 468-69 (1948)
28. GROSSMAN, M. I., ROBERTSON, C. R., AND IVY, A. C., *Am. J. Physiol.*, **153**, 1-9 (1948)
29. WOODWARD, E. R., BIGELOW, R. R., AND DRAGSTEDT, L. R., *Proc. Soc. Exptl. Biol. Med.*, **68**, 473-74 (1948)
30. JÖGI, P., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 206-11 (1949)
31. JÖGI, P., STRÖM, G., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 212-21 (1949)
32. MORTON, G. M., AND STAVRAKY, G. W., *Gastroenterology*, **12**, 808-20 (1949)
33. STAVRAKY, G. W., *Federation Proc.*, **8**, 151 (1949)
34. UVNÄS, B., *Acta Physiol. Scand.*, **15**, 427-37 (1948)
35. BABKIN, B. P., *Secretory mechanism of the digestive glands*, 900 pp. (P. Hoeber, New York, 1944)
36. EULER, U. S. v., *J. Physiol. (London)*, **107**, 10P-11P (1948)
37. KAHLSON, G., *Brit. Med. J.*, **II**, 1091-95 (1948)
38. WENER, J., KARP, D., AND HOFF, H. E., *Gastroenterology*, **11**, 923-29 (1948)
39. HANSON, M. E., GROSSMAN, M. I., AND IVY, A. C., *Am. J. Physiol.*, **153**, 242-58 (1948)
40. GROSSMAN, M. I., AND ROBERTSON, C. R., *Proc. Soc. Exptl. Biol. Med.*, **68**, 550-52 (1948)
41. ZWEIG, M., MEYER, K. A., AND STEIGMANN, F., *Gastroenterology*, **12**, 586-96 (1949)
42. CRIDER, R. J., AND WALKER, S. M., *Arch. Surg.*, **57**, 9-17 (1948)
43. SCHLESINGER, R. B., STEIGMANN, F., AND HARDT, L. L., *Federation Proc.*, **8**, 330-31 (1949)
44. ROBERTSON, C. R., AND IVY, A. C., *Federation Proc.*, **8**, 133 (1949)

45. SCHACHTER, M., *Am. J. Physiol.*, **156**, 248-55 (1949)
46. KAULBERSZ, J., AND BILSKI, R., *Federation Proc.*, **8**, 84 (1949)
47. LOGAN, V. W., *Gastroenterology*, **12**, 671-76 (1949)
48. HUNT, J. N., AND SPURRELL, W. R., *J. Physiol. (London)* **107**, 245-50 (1948)
49. CODE, C. F., LIVERMORE, G. R., RATKE, H. V., AND BLACKBURN, C. M., *Am. J. Physiol.*, **155**, 430-31 (1948)
50. BLICKENSTAFF, D., AND GROSSMAN, M. I., *Federation Proc.*, **8**, 12 (1949)
51. HOWAT, H. T., AND SCHOFIELD, B., *J. Physiol. (London)* **107**, 30P-31P (1948)
52. UVNÄS, B., *Acta Physiol. Scand.* **15**, 1-5 (1948)
53. VISSCHER, F. E., AND GROSSMAN, M. I., *Am. J. Physiol.*, **155**, 474 (1948)
54. KAULBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J., AND SALTZSTEIN, H. C., *Rev. Gastroenterol. (N. Y.)* **16**, 257-59 (1949)
55. KAULBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J., AND SALTZSTEIN, H. C., *Rev. Gastroenterol. (N. Y.)* **16**, 254-56 (1949)
56. SANDWEISS, D. J., KAULBERSZ, J., PATTERSON, T. L., AND SALTZSTEIN, H. C., *Federation Proc.*, **8**, 138 (1949)
57. PATTERSON, T. L., KAULBERSZ, J., SANDWEISS, D. J., AND SALTZSTEIN, H. C., *Federation Proc.*, **8**, 124-25 (1949)
58. GERSHBEIN, L. L., MILLEN, H. M., AND IVY, A. C., *Federation Proc.*, **8**, 56 (1949)
59. FERAYORNI, R. R., CODE, C. F., AND MORLOCK, C. G., *Gastroenterology*, **11**, 730-39 (1948)
60. KIRSNER, J. B., LEVIN, E., AND PALMER, W. L., *Proc. Soc. Exptl. Biol. Med.*, **70**, 685-88 (1949)
61. KIRSNER, J. B., LEVIN, E., AND PALMER, W. L., *Proc. Soc. Exptl. Biol. Med.*, **68**, 90-91 (1948)
62. KIRSNER, J. B., LEVIN, E., AND PALMER, W. L., *Proc. Soc. Exptl. Biol. Med.*, **69**, 108-11 (1948)
63. CODE, C. F., RATKE, H. V., LIVERMORE, G. R., JR., AND LUNDBERG, W., *Federation Proc.*, **8**, 26-27 (1949)
64. BLACKBURN, C. M., AND CODE, C. F., *Am. J. Physiol.*, **155**, 427 (1948)
65. GROSSMAN, M. I., AND ROBERTSON, C. R., *Am. J. Physiol.*, **153**, 447-53 (1948)
66. NELIGH, R. B., HOLT, J. F., LYONS, R. H., HOOBLER, S. W., AND MOE, G. K., *Gastroenterology*, **12**, 275-89 (1949)
67. ZWEIG, M., STEIGMANN, F., AND MEYER, K. A., *Gastroenterology*, **11**, 200-7 (1948)
68. ROBERTSON, C. R., AND GROSSMAN, M. I., *Am. J. Physiol.*, **155**, 464 (1948)
69. CAYER, D., LITTLE, J. M., AND YEAGLEY, J., *Gastroenterology*, **12**, 219-24 (1949)
70. FERRER, J. M., *Surg. Gynecol. Obstet.*, **87**, 76-78 (1948)
71. LEHMANN, G., AND STEFKO, P. L., *J. Lab. Clin. Med.*, **34**, 372-79 (1949)
72. GILG, E., *Acta Pharmacol. Toxicol.* **4**, 81-86 (1948)
73. FITZGERALD, O., AND MURPHY, P., *Nature*, **162**, 896-97 (1948)
74. UVNÄS, B., *Acta Physiol. Scand.*, **15**, 438-45 (1948)
75. HUNT, J. N., *J. Physiol. (London)*, **107**, 365-71 (1948)
76. BUCHER, G. R., GROSSMAN, M. I., AND IVY, A. C., *Gastroenterology*, **5**, 501-11 (1945)

77. MIRSKY, I. A., BLOCK, S., OSHER, S., AND BROH-KAHN, R. H., *J. Clin. Invest.*, **27**, 818-24 (1948)
78. BROH-KAHN, R. H., PODORE, C. J., AND MIRSKY, I. A., *J. Clin. Invest.*, **27**, 825-33 (1948)
79. PODORE, C. J., BROH-KAHN, R. H., AND MIRSKY, I. A., *J. Clin. Invest.*, **27**, 834-39 (1948)
80. BUCHER, G. R., AND ANDERSON, A., *Am. J. Physiol.*, **153**, 454-57 (1948)
81. BUCHER, G. R., *Federation Proc.*, **8**, 18 (1949),
82. GLASS, G. B. J., AND BOYD, L. J., *Gastroenterology*, **12**, 821-78 (1949)
83. GROSSBERG, A., KOMAROV, S. A., AND SHAY, H., *Federation Proc.*, **8**, 62 (1949)
84. HOLLANDER, F., AND KRAUS, S. D., *Federation Proc.*, **8**, 76-77 (1949)
85. CRIDER, R. J., AND WALKER, S. M., *Arch. Surg.*, **57**, 1-9 (1948)
86. HOLM, B., BOYARSKY, S., AND MORRIONE, T. G., *Gastroenterology*, **12**, 116-21 (1949)
87. DREYER, N. B., AND LEONARD, C. S., *Arch. intern. pharmacodynamie*, **78**, 86 (1949)
88. STEIN, I. F., JR., AND MEYER, K. A., *Surg. Gynecol. Obstet.*, **87**, 188-96 (1948)
89. HOLLANDER, F., *Gastroenterology*, **11**, 419-25 (1948)
90. GULLICKSON, M. J., AND CAMPBELL, D. A., *Gastroenterology*, **12**, 454-66 (1949)
91. POSTLETHWAIT, R. W., HILL, H. V., JR., CHITTUM, J. R., AND GRIMSON, K. S., *Ann. Surg.*, **128**, 184 (1948)
92. MACHELLA, T. E., AND LORBER, S. H., *Gastroenterology*, **11**, 426-41 (1948)
93. STEIN, I. F., JR., MEYER, K. A., AND STEIGMANN, F., *Surg. Gynecol. Obstet.*, **87**, 465-71 (1948)
94. THOMAS, J. E., AND KOMAROV, S. A., *Gastroenterology*, **11**, 413-18 (1948)
95. BERG, M., *Am. J. Digestive Diseases*, **16**, 35-55 (1949)
96. SALTZSTEIN, H. C., SANDWEISS, D. J., HILL, E. J., AND HAMMER, J., *Gastroenterology*, **12**, 122-32 (1949)
97. FRIESEN, S. R., MERENDINO, K. A., BARONOFKY, I. D., MEARS, F. B., AND WANGENSTEEN, O. H., *Surgery*, **24**, 134-59 (1948)
98. WANG, K. J., AND GROSSMAN, M. I., *Am. J. Physiol.*, **155**, 476 (1948)
99. WENER, J., HOFF, H. E., AND SIMON, M. A., *Gastroenterology*, **11**, 904-22 (1948)
100. HANSON, M. E., GROSSMAN, M. I., AND IVY, A. C., *Surgery*, **24**, 844-51 (1948)
101. MCCORRISTON, J. R., WEBSTER, D. R., AND MACKENZIE, D. W., *Proc. Soc. Exptl. Biol. Med.*, **70**, 637-43 (1949)
102. LILLEHEI, C. W., AND WANGENSTEEN, O. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 369-72 (1948)
103. TRABUCCHI, E., *Arch. intern. pharmacodynamie*, **78**, 129-43 (1949)
104. POTH, E. J., MANHOFF, L. J., DELOACH, A. W., *Surgery*, **24**, 62-69 (1948)
105. HALE, E. H., AND GROSSMAN, M. I., *J. Lab. Clin. Med.*, **34**, 228-33 (1949)
106. FOGELMAN, M. J., GROSSMAN, M. I., AND IVY, A. C., *Surgery*, **25**, 60-67 (1949)
107. SHAY, H., GRUENSTEIN, M., AND SIFLET, H., *Proc. Soc. Exptl. Biol. Med.*, **69**, 369-73 (1948)
108. MCGINTY, D. A., WILSON, M. L., AND RODNEY, G., *Proc. Soc. Exptl. Biol. Med.*, **70**, 334-36 (1949)
109. HOLM, B., AND MACKAY, A. G., *Surgery*, **25**, 446-50 (1949)

110. VISSCHER, F. E., AND LYSTER, S. C., *Federation Proc.*, **8**, 159 (1949)
111. MAGEE, D. F., KIM, K. S., AND IVY, A. C., *Federation Proc.*, **8**, 103 (1949)
112. HARTIALA, K., AND GROSSMAN, M. I., *Federation Proc.*, **8**, 69 (1949)
113. SCHILLING, J. A., AND PEARSE, H. E., *Surg. Gynecol. Obstet.*, **87**, 225-34 (1948)
114. WANGENSTEEN, O. H., SANCHEZ, H., AND SAKO, Y., *Am. J. Physiol.*, **155**, 476 (1948)
115. SANCHEZ-PALOMERA, E., AND WANGENSTEEN, O. H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 327-30 (1948)
116. GRANT, R., *Federation Proc.*, **8**, 59 (1949)
117. LEVIN, E., KIRSNER, J. B., PALMER, W. L., AND BUTLER, C., *Gastroenterology*, **10**, 939-51 (1948)
118. LEVIN, E., KIRSNER, J. B., PALMER, W. L., AND BUTLER, C., *Gastroenterology*, **10**, 952-64 (1948)
119. LEVIN, E., KIRSNER, J. B., AND PALMER, W. L., *Proc. Soc. Exptl. Biol. Med.*, **69**, 153-56 (1948)
120. KIRSNER, J. B., LEVIN, E., AND PALMER, W. L., *Gastroenterology*, **11**, 598-617 (1948)
121. RICKETTS, W. E., PALMER, W. L., KIRSNER, J. B., AND HAMANN, A., *Gastroenterology*, **11**, 789-806 (1948)
122. WINKELSTEIN, A., AND HESS, M., *Gastroenterology*, **11**, 326-36 (1948)
123. ANNEGERS, J. H., AND FRIEND, F., *Federation Proc.*, **8**, 4-5 (1949)
124. CANTAROW, A., WIRTS, C. W., SNAPE, W. J., AND MILLER, L. L., *Am. J. Physiol.*, **154**, 211-19 (1948)
125. GROSSMAN, M. I., JANOWITZ, H. D., RALSTON, H., AND KIM, K. S., *Gastroenterology*, **12**, 133-38 (1949)
126. WANG, C. C., AND GROSSMAN, M. I., *Am. J. Physiol.*, **156**, 256-60 (1949)
127. FREEMAN, S., *Surg. Gynecol. Obstet.*, **87**, 735-38 (1948)
128. POPPER, H. L., AND NECHELES, H., *Am. J. Digestive Diseases*, **15**, 359-63 (1948)
129. THOMAS, J. E., *Rev. Gastroenterol. (N. Y.)*, **11**, 813-20 (1948)
130. MEYER, K. H., FISCHER, E. H., BERNFELD, P., AND DUCKERT, F., *Arch. Biochem.*, **18**, 203-5 (1948)
131. LANE, R. L., AND WILLIAMS, R. J., *Arch. Biochem.*, **19**, 329-35 (1948)
132. BURN, J. H., AND HOLTON, P., *J. Physiol. (London)*, **107**, 440-55 (1948)
133. GERSHBEIN, L. L., WANG, C. C., AND IVY, A. C., *Proc. Soc. Exptl. Biol. Med.*, **70**, 516-21 (1948)
134. WANG, C. C., GROSSMAN, M. I., AND IVY, A. C., *Am. J. Physiol.*, **154**, 358-68 (1948)
135. WALDRON, J. M., THOMAS, J. E., AND TKACZ, L. P., *Federation Proc.*, **8**, 161 (1949)
136. ROUTLEY, E. F., BOLLMAN, J. L., AND GRINDLAY, J. H., *Am. J. Physiol.*, **155**, 465 (1948)
137. FRIEDMAN, M. H. F., AND SNAPE, W. J., *Proc. Soc. Exptl. Biol. Med.*, **70**, 280-83 (1949)
138. DREILING, D. A., AND HOLLANDER, F., *Gastroenterology*, **11**, 714-29 (1948)
139. DORNBERGER, G. R., COMFORT, M. W., WOLLAEGER, E., AND POWER, M. H., *Gastroenterology*, **11**, 701-13 (1948)

140. KNIGHT, W. A., JR., MUETHER, R. D., AND SOMMER, A. J., *Gastroenterology*, **12**, 34-48 (1949)
141. BAGGENSTOSS, A. H., POWER, M. H., AND GRINDLAY, J. H., *Gastroenterology*, **11**, 208-20 (1948)
142. NOTHMAN, M. M., PRATT, T. D., AND BENOTTI, J., *J. Lab. Clin. Med.*, **33**, 833-40 (1949)
143. LIUM, R., AND MADDOCK, S., *Surgery*, **24**, 593-604 (1948)
144. POPPER, H. L., NECHELES, H., AND RUSSELL, K. C., *Surg. Gynecol. Obstet.*, **87**, 79-82 (1948)
145. POPPER, H. L., *Surg. Gynecol. Obstet.*, **88**, 254-58 (1949)
146. WHEELER, J. E., LUKENS, F. D. W., AND GYORGY, P., *Proc. Soc. Exptl. Biol. Med.*, **70**, 187-89 (1949)
147. WANG, C. C., WANG, K. J., AND IVY, A. C., *Federation Proc.*, **8**, 161 (1949)
148. STEGGARDA, F. R., AND CLARK, W. C., *Federation Proc.*, **8**, 151 (1949)
149. STEGGARDA, F. R., AND CLARK, W. C., *Am. J. Physiol.*, **155**, 470-71 (1948)
150. POSEY, E. L., BARGEN, J. A., DEARING, W. H., AND CODE, C. F., *Gastroenterology*, **11**, 344-56 (1948)
151. QUIGLEY, J. P., in *Medical Physics*, 1744 pp., (Yearbook Publishers, Chicago, 1943)
152. HWANG, K., GROSSMAN, M. I., AND IVY, A. C., *Am. J. Physiol.*, **154**, 343-57 (1948)
153. CHILD, G. P., AND WOODBURY, R. A., *Federation Proc.*, **8**, 281 (1949)
154. CRAVER, B. N., BARRETT, W., CAMERON, A., EARL, A., AND ROTH, F., *Federation Proc.*, **8**, 283-84 (1949)
155. LORBER, S. H., AND MACHELLA, T. E., *Gastroenterology*, **12**, 57-69 (1949)
156. HIGGINS, J. R., SCHOEN, A. M., AND KNOEFEL, P. K., *Gastroenterology*, **11**, 508-18 (1948)
157. CHILD, G. P., *Federation Proc.*, **8**, 281 (1949)
158. FELDBERG, W., AND LIN, C. Y., *J. Physiol.*, **107**, 37P-38P (1948)
159. DODDS, D. C., OULD, C. L., AND DAILEY, M. E., *Gastroenterology*, **10**, 1007-9 (1949)
160. LANE, A., ROBERTSON, C. R., AND GROSSMAN, M. I., *Federation Proc.*, **8**, 91 (1949)
161. LONGINO, F. H., CHITTUM, J. R., AND GRIMSON, K. S., *Proc. Soc. Exptl. Biol. Med.*, **70**, 467-75 (1948)
162. HALBEISEN, W. A., GRUBER, C. M., JR., AND GRUBER, C. M., *Proc. Soc. Exptl. Biol. Med.*, **68**, 343-45 (1948)
163. LOUCKES, H., BRODY, D. A., AND QUIGLEY, J. P., *Federation Proc.*, **8**, 100 (1949)
164. LORBER, S. H., KOMAROV, S. A., AND SHAY, H., *Federation Proc.*, **8**, 99 (1949)
165. HIGHTOWER, N. C., CODE, C. F., MAHER, F. T., AND MORLOCK, C. G., *Federation Proc.*, **8**, 75 (1949)
166. STICKNEY, J. C., NORTHUP, D. W., AND VAN LIERE, E. J., *Am. J. Physiol.*, **155**, 471 (1948)
167. NORTHUP, D. W., AND VAN LIERE, E. J., *J. Pharm. Exptl. Therap.*, **93**, 208-9 (1948)
168. POSEY, E. L., JR., BROWN, H. S., AND BARGEN, J. A., *Gastroenterology*, **11**, 83-89 (1948)

169. DOUGLAS, D. M., *J. Physiol. (London)*, **107**, 472-78 (1948)
170. LOOMIS, T., *Proc. Soc. Exptl. Biol. Med.*, **69**, 146-50 (1948)
171. KRUEGER, H., *Federation Proc.*, **8**, 310 (1949)
172. WHITROCK, R. M., TIECHE, H. L., AND SEEVERS, M. H., *Am. J. Physiol.*, **155**, 477-78 (1948)
173. WATKINS, D. H., AND MANN, F. C., *Am. J. Physiol.*, **155**, 476 (1948)
174. FAIK, S., MANN, F. C., AND GRINDLAY, J. H., *Am. J. Physiol.*, **155**, 436 (1948)
175. CRAVER, B. N., CAMERON, A., AND YONKMAN, F. F., *J. Pharm. Exptl. Therap.*, **93**, 168-74 (1948)
176. CRAVER, B. N., AND CAMERON, A., *Arch. intern. pharmacodynamie*, **78**, 582-90 (1949)
177. AMBACHE, N., *J. Physiol. (London)*, **104**, 266-87 (1946)
178. EMMELIN, N., AND FELDBERG, W., *J. Physiol. (London)*, **106**, 482-502 (1947)
179. ERSPAMER, V., AND PAOLINI, A., *Arch. intern. pharmacodynamie*, **77**, 415-33 (1948)
180. ALMY, T. P., KERN, F., AND TULIN, M., *Gastroenterology*, **12**, 425-36 (1949)
181. ALMY, T. P., HINKLE, L. E., JR., BERLE, B., AND KERN, F., *Gastroenterology*, **12**, 437-49 (1949)
182. GASTON, E. A., *Surg. Gynecol. Obstet.*, **87**, 280-90 (1948)
183. WEEKS, J. R., AND CHENOWETH, M. B., *Federation Proc.*, **8**, 345 (1949)
184. FARAH, A., ANGEL, R., AND WEST, T. C., *Federation Proc.*, **8**, 290 (1949)
185. EWING, P. L., SCHLENK, F., AND EMERSON, G. A., *Federation Proc.*, **8**, 290 (1949)
186. BEAN, J. W., AND MOHAMED, M. S., *Federation Proc.*, **8**, 9 (1949)
187. MOHAMED, M. S., AND BEAN, J. W., *Federation Proc.*, **8**, 111-12 (1949)
188. COLLINS, D. A., *J. Pharm. Exptl. Therap.*, **94**, 244-48 (1948)
189. ALTHAUSEN, T. L., *Gastroenterology*, **12**, 467-80 (1949)
190. HEERSMA, J. R., AND ANNEGERS, J. H., *Proc. Soc. Exptl. Biol. Med.*, **69**, 140-41 (1948)
191. CLARKE, B. G., IVY, A. C., AND GOODMAN, D., *Am. J. Physiol.*, **153**, 264-67 (1948)
192. POPPER, H., STEIGMANN, F., AND DYNIEWICZ, H. A., *Gastroenterology*, **10**, 987-1000 (1948)
193. POPPER, H., AND VOLK, B. W., *Proc. Soc. Exptl. Biol. Med.*, **68**, 562-64 (1948)
194. KAREL, L., AND FLEISHER, J. H., *Am. J. Physiol.*, **153**, 268-76 (1948)
195. KAREL, L., *Physiol. Revs.*, **28**, 433-50 (1948)
196. ROBINSON, C. S., BUCHER, G. R., AND DZIEWIATKOWSKI, D., *Federation Proc.*, **8**, 243 (1949)
197. BUCHER, G. R., ANDERSON, C. E., AND ROBINSON, C. S., *Federation Proc.*, **8**, 188 (1949)
198. ALTHAUSEN, T. L., UYEYAMA, K., AND SIMPSON, R. G., *Gastroenterology*, **12**, 795-807 (1949)
199. THOMAS, J. E., *Gastroenterology*, **12**, 545-60 (1949)
200. UVNÄS, B., *Acta. Physiol. Scand.*, **15**, 362-64 (1948)
201. BARCLAY, A. E., AND BENTLEY, F. H., *Gastroenterology*, **12**, 177-83 (1949)
202. HARTMANN, J. F., AND WELLS, L. J., *Proc. Soc. Exptl. Biol. Med.*, **68**, 327-30 (1948)
203. HARE, W. V., AND STEWART, H. L., *Federation Proc.*, **8**, 357 (1949)

204. PHILLIPSON, A. T., *J. Physiol. (London)*, **107**, 21P-22P (1948)
205. McDONALD, I. W., *J. Physiol. (London)*, **107**, 21P (1948)
206. JEFFERSON, N. C., PHILLIPS, C. W., LEVINE, R., AND NECHELES, H., *Federation Proc.*, **8**, 81-82 (1949)
207. GRANT, R., GROSSMAN, M. I., AND IVY, A. C., *Am. J. Physiol.*, **155**, 440 (1948)
208. MILLER, J. R., HERRICK, J. F., MANN, F. C., GRINDLAY, J. H., AND PRIESTLY, J. T., *Am. J. Physiol.*, **155**, 455 (1948)
209. BLICKENSTAFF, D., AND GROSSMAN, M. I., *Am. J. Physiol.*, **155**, 427-28 (1948)
210. WOLF, S., *Gastroenterology*, **12**, 212-18 (1949)
211. BORISON, H. L., *Am. J. Physiol.*, **155**, 428 (1948)
212. BORISON, H. L., AND WANG, S. C., *Federation Proc.*, **8**, 13 (1949)
213. LASICHAK, A. G., AND LEVEY, S., *Proc. Soc. Exptl. Biol. Med.*, **70**, 74-76 (1949)
214. SCHIFF, C. A., GOLDBERG, S. L., AND NECHELES, H., *Surgery*, **25**, 257-67 (1949)
215. NEMIR, P., JR., HAWTHORNE, H. R., AND LECRONE, B. L., *Proc. Soc. Exptl. Biol. Med.*, **69**, 14-16 (1948)
216. DRYE, J. C., *Surg. Gynecol. Obstet.*, **87**, 472-75 (1948)
217. CARLSON, A. J., AND HOELZEL, F., *Gastroenterology*, **12**, 108-15 (1949)
218. KIRK, E., *Gastroenterology*, **12**, 782-94 (1949)
219. POGRUND, R. S., AND STEGGARDA, F. R., *Am. J. Physiol.*, **153**, 475-82 (1948)
220. BLOOMFIELD, A. L., AND LEW, W., *Proc. Soc. Exptl. Biol. Med.*, **69**, 11-14 (1948)
221. GRACE, W. J., WOLF, S., AND WOLFF, H. G., *Am. J. Med. Sci.*, **217**, 241-51 (1949)
222. WENER, J., HOFF, H. E., AND SIMON, M. A., *Gastroenterology*, **12**, 637-47 (1949)
223. SCARBOROUGH, H., ELKIN, M., BLISS, H. A., PARK, H. W., AND LANDIS, E. M., *Am. J. Physiol.*, **155**, 467 (1949)
224. HOPPE, J. D., AND ARCHER, S., *Federation Proc.*, **8**, 303-4 (1949)
225. SNAPE, W. J., FRIEDMAN, M. H. F., AND SWENSON, P. C., *Am. J. Med. Sci.*, **216**, 188-94 (1948)
226. ANTIA, F., AND IVY, A. C., *Federation Proc.*, **8**, 5 (1949)
227. DANIELSON, W. H., BRINKLEY, E. L., AND PALMER, H. D., *Pediatrics*, **3**, 645-50 (1949)
228. DAVIS, R. E., AND IVY, A. C., *Cancer*, **2**, 138-43 (1949)

## THE COAGULATION OF BLOOD AND HEMOSTASIS<sup>1,2</sup>

BY ARMAND J. QUICK

*Department of Biochemistry, Marquette University School of Medicine  
Milwaukee, Wisconsin*

Since the number of papers on coagulation has greatly increased, the reviewer, in order to avoid merely cataloging them with telegraphic brevity, was compelled to select mainly those which contribute specifically to the physiology of blood clotting. In several instances, it was necessary to depend on experimental studies from the writer's own laboratory to evaluate certain researches, especially because of an increasing uncritical reliance on purified reagents. Serious errors have arisen from failure to realize that products made from blood collected in a slaughter house may be quite different from the true physiological components that function in the organism.

### HEMOSTASIS

Hemostasis is a complicated mechanism composed of various co-ordinated reactions of which the formation of fibrin is the best known. According to Chen & Tsai (1) arterial hemostasis consists of a constriction and a coagulation phase. The constriction is dependent upon a nervous reflex, a local muscular response, and pressor substances liberated from disintegrating platelets. Capillary hemostasis is dependent mainly upon adhesion of the vessel wall following endothelial injury. Humble (2) found that in petechial hemorrhage, the defect is at the arteriolar end of the capillary loop. The vasospasm following occlusions, which often persist after release of the occlusion, observed by Laufman (3) is no doubt a manifestation of the hemostatic response. Zucker (4), by direct *in vivo* observations, found that cut vessels contract first by traumatic stimulation of the vascular smooth muscle and that this is followed by generalized vasoconstriction in the area due to sub-

<sup>1</sup> This review covers the period from July 1, 1947 to July 1, 1949.

<sup>2</sup> Since this review is a continuation of the one written by Smith & Flynn two years ago, the references which they cited will not be repeated when the subject matter is mentioned in the text. All references not found in the bibliography will be found in previous editions of the *Annual Review of Physiology*.

stances liberated from disintegrating platelets. The initial reflex contractions of the injured vessel occur in heparinized and dicumarolized animals, but platelet agglutination becomes defective, and the generalized vasoconstriction is absent. A renewed interest in the vasoconstricting function of the platelet is being manifested. Brun (5, 6) found that serum applied locally exerts a strong constricting action on arteriols of the skin, muscles, and mesentery. A curious variation in the response of the vessels of different tissues occurs. This serum vasoconstrictor agent, more powerful than epinephrine, which appears to arise from platelet lysis, has been isolated in crystalline form by Rapport, Green & Page (7, 8) and named serotonin. An inactivator has been prepared from lung tissue (9).

#### THEORIES OF BLOOD COAGULATION

During the past few years, new ideas have been developed which challenge a number of important accepted concepts, including the classical theory which states that prothrombin is converted to thrombin by the action of ionic calcium and thrombokinase. This theory fails to explain the autocatalytic nature of the clotting reaction, offers no explanation for the source of thrombokinase, and does not define the function of the platelets. Many workers still accept the view that platelets supply thromboplastin, but a school started by Lenggenhager and joined by Astrup, Laki, Wiedenbauer, Reichl, Breda, Lozner & Taylor, and Milstone (10) believes that thromboplastin exists in plasma in an inactive form which, by autocatalysis, probably through a rough surface, is converted to the active form independent of platelets. More recently Milstone (11) has recognized that platelets together with a globulin cofactor play a part in activating prothrombin. Conley *et al.* (12) admit the need of platelets in coagulation, but adhere to the idea of surface catalysis for the conversion of the thromboplastin precursor.

With the introduction of a silicone which produces a surface that preserves platelets, it was found that the removal of these cells by centrifuging produces a plasma in which coagulation is delayed or abolished (13, 14, 15). Quick (14) found that when platelet poor plasma clotted, little prothrombin was consumed. Both Brinkhous (13) and Quick observed that hemophilic platelets bring about nor-

mal coagulation in deplateletized nonhemophilic plasma. Brinkhous postulated that hemophilic plasma lacks a platelet lysin and that, therefore, these cells fail to liberate their thromboplastin. Quick found that platelets contain very little thromboplastin—a finding later confirmed by Ware, Fahey & Seegers (16). According to Quick, the platelets on lysis produce an enzyme which activates the precursor, thromboplastinogen. The enzymatic nature of the platelet factor is shown by the fact that as the number of these cells increases, the speed of prothrombin conversion is accelerated, but the final amount is approximately the same (17).

A new theory of coagulation has been offered (18, 19). Plasma thromboplastinogen is activated by an enzyme resulting from platelet lysis. The active thromboplastin reacts stoichiometrically with the prothrombin complex, which includes bound calcium, to form thrombin. Not only does thrombin change fibrinogen to fibrin, but it also labilizes platelets, thereby initiating a chain reaction. This thrombinogenic cycle has as its cardinal driving forces thrombin formation and platelet lysis. A lack of platelets or any agent which removes thrombin, or any deficiency, such as the lack of thromboplastinogen in hemophilia, which causes a decrease in thrombin formation, breaks the chain reaction. The most important remover of thrombin according to Quick & Favre-Gilly (20) is the fibrin of the clot itself. Only a minute amount of prothrombin is consumed during the time that all the fibrinogen is clotted. The authors postulate that the fibrin clot serves to moderate and control the chain reaction. That thrombin affects the platelets is demonstrated by the marked retraction occurring when thrombin is added to native hemophilic plasma, and also by the observation of Zatti (21) that thrombin causes agglutination of platelets in citrated blood.

#### PROTHROMBIN

*The factors in the complex.*—Since the discovery in 1943 by Quick and the following year by Owren of a new factor essential for prothrombin activity, a confusing array of findings has been reported. Fantl & Nance in 1946 announced the discovery of an accelerator factor. Seegers and his associates, who had steadfastly defended the unitary concept of prothrombin activity, reported in 1947 a new agent which accelerated the activation of prothrombin

and emphasized that it was different from Quick's factor. They named the new agent Ac-globulin (22) and reported that by means of an optimum amount of this substance, they obtained as high as 23,000 units of thrombin per mg. tyrosine, which represented a yield of more than 50 per cent over their old method of activation. They stated that when activation of prothrombin is delayed, the thrombin yield is diminished. With that statement, they unwittingly discredited many of the results previously obtained by the two stage method, since the procedure contained no provisions for an optimal or even a controlled amount of Ac-globulin. Later (23) they concluded that there are two Ac-globulins, one present in plasma, the other in serum. Thrombin converts the former to the serum type, and this agent catalyzes the formation of thrombin. In another paper Seegers and his group (24) again emphasized that Ac-globulin is stable in oxalated bovine plasma and reattacked Quick's explanation that the decrease in prothrombin activity during storage is due to deterioration of a labile factor. Their eagerness to show that the Ac-globulin is not identical with the labile factor is carried over to another paper (25). They pointed out that Ac-globulin is adsorbed by magnesium hydroxide and aluminum hydroxide whereas the labile factor is not. A quantitative method for Ac-globulin based on the two stage procedure is described. The electrophoretic mobility is reported as  $-4.73 \times 10^{-5}$  in phosphate buffer at pH 7.4.

As a further development of their theory, Ware & Seegers (26) committed themselves to the view that plasma Ac-globulin is inert and is probably a proenzyme which requires thrombin as an activator. Their evidence is none too clear. The finding of Sykes, Seegers, & Ware (27) that experimental liver damage diminishes both prothrombin and Ac-globulin is in agreement with the earlier work of Munro, Hart, Munro & Walkling, who reported that both components of prothrombin drop after hepatectomy. Ware & Seegers (28) found that small amounts of thrombin destroy relatively large quantities of prothrombin, but such inactivated prothrombin can regenerate. In this paper, they still maintained that thromboplastin and calcium alone can activate prothrombin; but more recently they reported (29) that when they dissolve purified prothrombin in 30 per cent sodium citrate, it converts spontaneously to thrombin.

A curious reversal of views can be noted in their later papers. Fahey, Ware & Seegers (30) half-heartedly admitted that their Ac-globulin may be the same as Quick's factor. They found that Ac-globulin in oxalated plasma decreases more rapidly than in citrated plasma, thus confirming the findings of Quick, who pointed out that removal of calcium ions exerts a major influence on the stability of the labile factor. The labile factor diminishes in stored amberlite plasma (31). The failure of Honorato and his co-workers (32) to observe this must be ascribed to a defective reagent. Particularly interesting and clarifying is the finding of Murphy & Seegers (33) that human plasma has a low level of Ac-globulin while dog plasma contains approximately 12 times and rabbit 15 times more. They thus confirm the observation of Stefanini & Quick (34, 35), who found that rabbit plasma contains 50 times and dog plasma 10 times as much as that of man. These authors describe a simple method for assaying the labile factor using stored human plasma as the medium. Fantl & Everard (36), with a different method of assay, also found that rabbit plasma contains 50 times more than human plasma, provided they used tissue thromboplastin. With Russell viper venom this difference could not be demonstrated.

Owing to the low concentration of labile factor in human plasma, its depletion during storage is readily detected, a fact now also recognized by Murphy, Ware & Seegers (37). No doubt the reason Seegers and his co-workers failed to recognize the lability of their Ac-globulin can be explained on the basis that they mainly used bovine plasma, which has a high content of this factor; and they probably stored large volumes of blood, which did not permit penetration of oxygen, which is responsible for the destruction of the labile factor.

There is now general agreement that loss of prothrombin in stored plasma is not due to changes in fibrinogen. Alexander & de Vries (38) have found the same decrease in prothrombin activity occurring in the plasma of an afibrinogenemic patient. Honorato & Quick (39) demonstrated that fibrinogen may be contaminated with the labile factor, which very likely explains why Loomis & Seegers went astray. Fantl & Nance (40) believed that in addition to loss of their factor, thrombin inhibitors form during storage. Honorato (41) and Stefanini (42) also noted an increase in anti-

thrombic activity, which is influenced by the type of anticoagulant employed. Munro & Munro (43) now believe that prothrombin itself is altered in storage by the inactivation of a labile group in the molecule. Honorato (41) postulated that the labile factor is a cofactor of thromboplastin. Favre-Gilly (44) suggested that it serves as cofactor to both prothrombin and thromboplastin.

Since both Owren (45) and Fantl (46) agree that their factors are identical with the labile factor and Ac-globulin, no further studies of comparison need to be discussed. Owren has reported further work on the purification and properties of his product. When Quick discovered this factor, he assumed that it functions stoichiometrically. Owren postulates that it is enzymatically acted upon by cytokinase (thrombokinese) and calcium to form factor VI or prothrombinase, which, with calcium, catalytically transforms prothrombin to thrombin. Fantl & Nance consider it an agent which accelerates the activation of prothrombin. Seegers and his associates accept Fantl's theory, but they postulate that the factor is inactive in blood and must be activated by thrombin. Quick & Stefanini (47) have shown that when the stable prothrombin, which they designated as component A, is treated with increasing amounts of labile factor, a minimum constant prothrombin time is obtained which excess labile factor does not alter, suggesting a stoichiometric type of reaction. Lewis & Ferguson (48), using purified reagents supplied to them by Seegers, have also obtained results which strongly suggest that Ac-globulin functions stoichiometrically.

In a further study, Quick & Stefanini (49) recorded findings which show that the stable factor or prothrombin in human plasma exists partly free and partly in a precursor state. The conversion of inactive prothrombin is accelerated by a rough surface such as glass; it is independent of thrombin or calcium, since it occurs in stored oxalated plasma; and it is not delayed in hemophilic or thrombocytopenic blood. Their work substantiates in part the concept of Bordet, who believed that all prothrombin in the blood existed in an inactive state. It appears highly probable that the existence of free and inactive prothrombin has been responsible for many puzzling results, especially since both forms are adsorbed by tricalcium phosphate. It seems very likely that the conversion of inactive prothrombin to the active form has been misinterpreted

as an acceleration of the activation of prothrombin to thrombin. Much of the recent researches of Alexander and his group may, perhaps, be reinterpreted by this new development. The factor which they call "serum prothrombin conversion factor" (50) is measured by determining the prothrombin time of a mixture of the serum, oxalated plasma, and barium sulfate treated plasma. It is likely that they are measuring how much prothrombin precursor is changed to the active form. They found that their factor is increased by mechanical agitation of fresh blood and by the addition of thromboplastin. Heparin, dicumarol, and silicone coated glassware cause decreased formation of the factor during coagulation (51, 52). In the clotting of thrombocytopenic blood, the serum retains a high prothrombin activity, but little of the factor is produced (53). When hemophilic blood clots, a similar result is noted (54). Jacox (55, 56) has also concluded that serum contains a prothrombin converting factor, but it is probable that he too was observing the conversion of inactive prothrombin to the active state. Mann and co-workers (57) reported that not only fresh plasma and serum but also a platelet extract potentiate the action of thromboplastin in stored plasma. It hardly seems likely that platelets should contain labile factor, although Ware *et al.* (16) report that they contain an accelerator similar to Ac-globulin. According to Mann & Hurn (58) a clotting factor other than prothrombin disappears when complement is inactivated by aging, zymine, or ammonia.

*The determination of prothrombin.*—The long dispute on the comparative accuracy of the one and two stage methods appears now in reach of an amiable settlement. According to Quick & Stefanini (49), the prothrombin time depends on the concentrations of the free prothrombin, the labile factor, thromboplastin, and calcium. Since the latter two are controlled, only variations in the free prothrombin and the labile factor influence the results of the one stage method. Lack of the labile factor can readily be estimated (35); and if below normal, it can be supplied as an additional reagent, as Frick & Koller (59, 60) have done, which does not change the fundamental basis of the test. The problem of determining free and total prothrombin is more complicated. For an absolutely accurate determination of free prothrombin, blood must be kept in silicone coated glassware, since glass surface catalyzes

the conversion of inactive to active prothrombin. The factor responsible for this conversion is not clearly defined. It is not taken out readily by the common adsorbants (49); therefore, such deprothrombinized plasmas are unreliable as diluents for preparing prothrombin curves, which is contrary to the recent recommendations of Alexander (61) and Conley & Morse (62). Since it is not known what effect dilution with saline has on the activation of the prothrombin precursor, it seems best to avoid diluting plasma, especially since a number of workers have found no advantage using diluted plasma (61, 63, 64). It is interesting to speculate how much the hyperprothrombinemia observed by Unger & Shapiro (65, 66) in diluted plasma can be attributed to activation of the prothrombin precursor.

A new procedure (49) for determining free prothrombin (component A) by adsorption with tricalcium phosphate, elution with sodium citrate, and assaying by the one stage technique in standard deprothrombinized plasma offers a promising new analytical tool. The two stage method has been modified by the addition of a standardized quantity of Ac-globulin (67). Since the manipulations required in the two stage procedure probably do convert all or most of the inactive prothrombin to the free state, the method measures only total prothrombin.

Since the most important practical application of the determination of prothrombin is in the control of dicumarol therapy, much importance attaches itself to the results obtained by the one and two stage methods. Quick, Honorato & Stefanini (68) have shown that when the prothrombin time in rabbits is reduced with dicumarol to 24 sec. heart puncture produces fatal cardiac hemorrhage; and Quick (69, 70) has studied two boys with congenital hypoprothrombinemia who have a consistent prothrombin time of 19 sec. and have a frank bleeding tendency. Three members of another family with a prothrombin time of 16 sec. have normal hemostasis. Similar studies with the two stage method to establish the bleeding level apparently have not been made. Hurn *et al.* (71) found that following dicumarol, the prothrombin in man, as measured by the one stage test, dropped much faster than with the two stage method. In 8 of 10 instances cited, the percentage of prothrombin was only one-third to one-half as high with the one stage as with the two stage test. Owen & Bollman (72) reported similar results in dogs. Mawson (73) also observed lower values when he

used Quick's unmodified test, but when he substituted Russell viper venom and lecithin, the results agreed with the two stage method. He cited one case of bleeding in which the prothrombin by the one stage was 34 per cent, whereas it was about 60 per cent with the two stage and with the venom-lecithin test. If Mawson's findings, that the results of the two stage method agree with the venom-lecithin test, are correct, the reliability of the two stage procedure in the control of dicumarol therapy will have to come under scrutiny, for there is considerable evidence accumulating that the prothrombin, as measured by the one stage method, using venom for thromboplastin, may show a relatively high prothrombin level, even in the presence of hemorrhage and when the level, as determined by Quick's method, is below the margin of safety [Wilson (74), Cheney (75), Lempert (76), Biggs & Macfarlane (77), James (78)]. Olwin (79, 80), however, reports that the two stage test is the more accurate and safer means to control dicumarol therapy. In his charts, the prothrombin level by the two stage test is much lower than with Quick's method. How much the increase in antithrombic activity, which Hurn *et al.* (71, 81) noted after dicumarol, influences Olwin's results apparently was not considered. In view of the urgent need for reliable control of dicumarol therapy, especially since more than 23 deaths due to this drug have been reported (82), a concerted effort should be made to settle this problem. Mention should be made that in liver disease, the two stage method may sometimes show a hypoprothrombinemia when the one stage test gives inconclusive results, according to Mann *et al.* (83).

*Dicumarol and prothrombin.*—It is agreed that avitaminosis K and dicumarol depress, mainly, the stable prothrombin, as Dam & Sondergaard (84, 85) showed experimentally and which Quick & Stefanini (47) have confirmed, thus invalidating Quick's earlier claim that different components were affected (70). Fahey, Olwin & Ware (86) reported that dicumarol depresses both prothrombin and Ac-globulin. Lein & Lein (87) found that lipids extracted from brain are relatively more active on dicumarolized prothrombin than is tissue thromboplastin, which leads them to conclude that an altered prothrombin is synthesized. MacMillan (88) believes dicumarol plasma lacks an accelerator different from Owren's factor V.

The hypoprothrombinemia due to dicumarol can be better

counteracted by vitamin K<sub>1</sub> oxide than by synthetic compounds [James *et al.* (89, 90)]. Quick & Stefanini (91) could not establish a difference between the natural and synthetic vitamin in chicks. Boyd & Warner (92) observed no detectable effect of synthetic vitamin K in counteracting dicumarol in the rat. Other substances, including vitamin P (93), nicotinamide (94) with ascorbic acid (95), appear to antagonize dicumarol. The occasional delayed action of dicumarol (96, 97) suggests that the drug may be stored. Quick's observation that dicumarol affects the fetus more than the mother has been verified by Kraus *et al.* (98) and Sachs & Labate (99), who report the death of a human fetus due to hemorrhage.

*Miscellaneous drugs affecting prothrombin.*—The report of Axtrup (100), Lewitus (101), and others that penicillin may cause hypoprothrombinemia warrants attention. The effect of the methyl xanthines remains unsettled. Blood & Patterson (102) and Holland & Gross (103) found no influence, while McCormick & Young (104) reported a transient rise of prothrombin and a persistent increase in Ac-globulin. Honorato & Lopetegui (105) reported that digitalis decreases the prothrombin time, but this is counteracted by dicumarol. Mushett (106) has investigated the antiprothrombinemic effect of sulfaquinoxaline. Fantl & Nance (107) have studied the action of 3,3-ethylidene-bis-(4-hydroxy coumarin). A similar related compound, the ethyl ester of 4-hydroxy coumarin acetic acid also known as tromexan, has been studied by Kaulla & Pulver (108, 109), Reinis & Kubik (110) and de Nicola (111). The latter observed that the calcium requirement for optimum prothrombin time increased. This he has also found true for dicumarol (112), thus confirming older work. The hypoprothrombinemic action of 2-phenylindane-dione-1,3 studied by Soulier & Gueguen (113) and Jaques *et al.* (114) is interesting because, according to Jaques, the action may be on factor V. Selander & Bernius (115) found that salicylates commonly reduce prothrombin in children. Jaques & Lepp (116) obtained findings which suggest that salicylates may be converted by bacterial action to a prothrombinopenic agent. Maddock *et al.* (117) and Walker *et al.* (118) confirmed earlier reports that excess vitamin A may produce hypoprothrombinemia. In chicks, this does not occur when vitamin K intake is controlled (91), which suggests that vitamin A may interfere with bacterial synthesis of vitamin K. The rapid hypoprothrombinemia pro-

duced by external intestinal lymph drainage in rats [Mann *et al.* (119)] shows the need of a continuous supply of vitamin K in certain animals. The greater susceptibility of the young to lack of vitamin K is again shown by the effect of sulfathiazol on old and young rats (120). Field (121) reported that a mammary tumor in rats caused resistance to dicumarol, even though the prothrombin is reduced. According to Van den Ostende (122), cervical cancers tend to cause hypoprothrombinemia. Doles (123) reported hypoprothrombinemia in acute coronary occlusion and, contrary to the general practice, administered vitamin K.

*Vitamin K.*—A simple diet to produce vitamin K deficiency in chicks is described and a method of assay is outlined by Quick & Stefanini (91). They reported that vitamin K can completely restore prothrombin activity in 4 hr. Glavind *et al.* (124) found vitamin K in human saliva; and Dam, with his workers, (125) observed that the vitamin K in the press juice of spinach is fairly stable and is present mostly in the chloroplasts.

*Congenital hypoprothrombinemia.*—Sufficient progress has been made to end the indiscriminate grouping of the congenital types with the idiopathic. Some of the latter respond to vitamin K as Heindl *et al.* (126) have shown in one case. In addition to the type described by Owren (267), in which Factor V or the labile factor is diminished, two other distinct congenital hypoprothrombinemias with normal labile factor have been studied by Quick (69, 70). The fact that the blood of the two types mutually correct each other made it appear that the stable prothrombin contained two factors. Recent work by Quick & Stefanini (49) shows that one type lacks both free and total prothrombin, whereas the second has a lowered level of free, but the total may be normal. A factor responsible for maintaining a normal ratio of active to total is lacking. This type is hereditary, and the fixed free prothrombin level may run through several generations. Hagen & Watson (127) have reported an extensive study of a severe case in which other members of the family show a mild reduction in the prothrombin level. The ratio of free to total prothrombin in the newborn needs investigation, for Randall & Randall (128) found that the prothrombin time of hypoprothrombinemic plasma of infants was abnormally shortened by normal plasma and serum, a finding similar to that of Quick & Stefanini (91) on k-avitaminotic chicks.

*Calcium.*—The firmly entrenched theory that it is ionized calcium acting as a catalyst that participates in coagulation is challenged. Quick (129), by means of blood decalcified with amberlite, presented evidence that calcium reacts stoichiometrically in the formation of thrombin. Quick & Stefanini (31) concluded that sodium citrate combines with prothrombin, thus making it no longer adsorbable by tricalcium phosphate and incapable of being converted to thrombin. The anticoagulant action of citrate is antiprothrombic. Sodium oxalate is a true decalcifying agent, but its action is slow. It appears that it removes calcium from a compound which requires this metal for its activity. The speed with which the labile factor loses activity is increased by decalcification. Stefanini & Quick (130) reported that strontium is active in coagulation, but much less so than calcium. Even magnesium has some potency, but requires excess thromboplastin. The inhibitory action of calcium, strontium, and magnesium is quantitatively similar; but barium has a more pronounced action. Stefanini (131) has described the purification of amberlite and has shown that this reagent has little effect other than removing calcium. Hargreaves (132) claimed that calcium accelerates coagulation by neutralizing the antithrombic action of plasma.

*Thrombin.*—According to Seegers & Ware (133), the molecular weight of thrombin is 77,000 while that of prothrombin is 140,000. Gerandas (134) concluded that thrombin is removed from blood by adsorption and enzymatic destruction. By slowly injecting thrombin, Jürgens & Studer (135) achieved complete afibrinogenemia. At this stage further injection of excess thrombin causes convulsions and fatal hemorrhage.

#### THROMBOPLASTIN

Thromboplastin is still an undefined entity. According to Quick (18), it exists free in tissues but occurs as a precursor (thromboplastinogen) in blood, which requires an activator derived from platelets. This precursor is lacking in hemophilia. An antagonist to the platelet enzyme may produce a hemophilic-like disease, such as was studied by Quick & Stefanini (136). Similar cases with a circulating anticoagulant, which is neither an antithrombin nor an antithromboplastin, was presented by Craddock & Lawrence (137) Soulier & Burstein (138), and Conley *et al.* (139). Craddock ex-

plained the cause as a possible isoimmunization against the anti-hemophilic globulin. It is interesting to speculate whether the action of soya bean inhibitor observed by Tagnon & Soulier (140) and others may not be on the platelet enzyme. Since Nikolaeva (141) has reported that platelets contain a proteolytic enzyme like trypsin, it is probable that these plasma proteolytic enzymes, studied extensively by Ferguson *et al.* (142), may act on thromboplastinogen, especially since they have found that the enzymes are thromboplastic only in the presence of calcium and a phospholipid factor.

Purification of thromboplastin remains disappointing. Garces *et al.* (143) made electrophoretic studies of tissue thromboplastin, which contains a thermostable lipoprotein and a thrombolabile globulin. A lipid with some activity can be extracted from tissues; and antioxidants, like hydroquinone, can, according to Lein & Lein (144), preserve its potency. Whether the thromboplastic agent in blood can be removed by high speed centrifugation remains unanswered, for Flynn at the 1949 Macy Conference on Blood Coagulation, reported that he observed many platelets in this thromboplastic residue. If the activity of this product is due to platelets, then the hypothromboplastinemia, reported by Holden *et al.* (145), following total body irradiation may be more accurately accounted for by thrombocytopenia.

Chargaff (146) reported beef lung thromboplastin incubated with purified prothrombin and calcium, and then recovered by high centrifugation, had more activity than it possessed initially. He interprets this as support for the enzymatic nature of thromboplastin. Much is left to be desired in the control of his experiment, including a consideration of the labile factor. Chargaff's thromboplastic protein is inhibited by sodium desoxycholate and several rare earth salts (147).

Lewis & Ferguson (148) found that when they employed fixed quantities of calcium, purified prothrombin, and Ac-globulin (both reagents supplied by Seegers), the amount of thrombin increased with the quantity of thromboplastin added until a maximum point was reached. These results are in accord with the findings of Mertz *et al.*, who concluded that thromboplastin acts stoichiometrically. Tocantins *et al.* (149) and Overman & Wright (150) have isolated lipids from brain which are strongly antithromboplastic. It is not known what role such agents play physiologically.

*The prothrombin consumption test.*—A test to determine the thromboplastic activity of plasma comparable to the prothrombin time test, which measures the composite prothrombin activity, has been developed and named the prothrombin consumption test (19). It depends on measuring the amount of prothrombin remaining in the serum after coagulation. With the discovery that the separation of the clot from serum either spontaneously or by centrifugation influences both the speed and quantity of prothrombin consumed (20), the test has been standardized in regard to centrifugation (151). Soulier (152, 153) has modified the test by allowing the prothrombin of the serum to be converted to thrombin, which he determines, instead of following the one stage technique of the original method. Quick and his associates, Soulier, and more recently Alexander *et al.* (154) have found poor consumption in hemophilia and in experimental and clinical thrombocytopenia. The test may not be positive in mild cases of hemophilia (155). Quick *et al.* (156) showed a true deficiency of free thromboplastin in thrombocytopenic purpura.

#### PLATELETS

*Structure.*—By means of the electronmicroscope, Bessis & Burstein (157) have found that platelets contain reticulated fibers and spherules. Guttmann (158) found no nuclear fragments, although nuclear material of megakaryocytes participate in their formation.

*Clot retraction.*—By means of mixing citrated plasma with varying amounts of a platelet concentrate, Fonio (159 to 161) has shown that the degree of retraction depends on the number of platelets. He ascribes the poor retraction in hemophilic plasma to qualitatively altered platelets. Quick, Shanberge & Stefanini (17) studied quantitatively the relation of clot retraction to the number of platelets by means of plasma collected in silicone-coated glassware. They found that the number of platelets determines both the speed and degree of retraction. Chavallier & Fiehrer (162) found that a small amount of kaolin added to plasma completely abolishes retraction. Hirschboeck (163) standardized the retraction of a drop of blood in castor oil and, by means of this test, has evidence that retraction appears to occur more rapidly in patients subject to thromboembolic diseases.

*Agglutination.*—In anaphylactic shock, clumping of platelets

with resulting thrombocytopenia occurs. The same condition can be produced by antiplatelet serum according to Cruz & da Silva (164). This agglutination of platelets can be so extensive that a generalized formation of platelet thrombi in the small arterioles and capillaries throughout the body can occur (165 to 169). Many drugs are known to induce thrombocytopenia. Ackroyd (170) has made a careful study of one of these drugs, allyl-isopropyl acetyl-carbamide, and reported that it produces *in vitro* agglutination of platelets of sensitized patients. The observation of Watson *et al.* (171) that estrogens can cause thrombocytopenic purpura should receive clinical recognition. Pohle & Cohen (172) and Madison (173) emphasized that allergy is a definite cause of thrombocytopenia.

The actual agent that causes agglutination of platelets is now known. Copley (174), who holds that heparin causes agglutination, has reported observing platelet thrombi in the hamsters' pouch due to this drug; and he has postulated (175) that the thrombocytopenia following ionizing irradiation is caused by heparin. This has led Fidler & Jaques (176) as well as Quick with his co-workers (177) to investigate the effect of commercial heparin *in vivo*. Fidler & Jaques observed a transient drop in man and dogs, but with highly purified samples the effect was slight. Quick *et al.* found no drop in man or rabbits, but a precipitous, though temporary, decrease in dogs. These findings make it appear unlikely that heparinemia is the cause of platelet agglutination in various types of shock, as postulated by Copley and also Fleck (178).

The relationship between platelet adhesiveness and agglutination is obtaining increasing attention. Weiner *et al.* (179) found the method of Wright for estimating adhesiveness satisfactory, while Morrison (180) uses merely the clumping, as observed in the routine blood film, as a guide of platelet adhesiveness. Moolten *et al.* (181) have developed a refined test which consists in determining the number of platelets removed by a standardized glass wool filter. Moolten believes that adhesiveness is brought about by an agent, thrombocytosin, derived from lipids of the body; while a factor from the spleen, thrombocytopen, antagonizes thrombocytosin and also suppresses the formation of platelets. Cruz and his associates (182) reported that urethane produces a marked thrombocytopenia. Reviews on platelets and purpura have been written

by Tocantins (183), Burstein & Bessis (184), and Croizat *et al.* (185).

#### INHIBITORS

Anticoagulants of diverse kinds have been postulated; but with the concept that thrombin is the key to the chain reaction of coagulation, the antithrombins deserve first consideration. With the finding that fibrin appears to be the most important physiological antithrombin (20), the commonly recognized antithrombin present in the albumin fraction of the serum may be relegated to a secondary position.

*Heparin.*—Although this substance is commonly called the natural anticoagulant, no good proof exists that it functions physiologically in maintaining the fluidity of the blood, although several workers such as Gerendas (186) and Barnard (187) have evolved theories on coagulation centering about heparin. Astrup (188) found that injection of thromboplastin did not stimulate the production of heparin, thus making it appear unlikely that it responds as a physiological anticoagulant. The occurrence of heparin normally in blood is still a moot question which is discussed editorially by Tocantins (189). According to Conley (190) and Monkhouse *et al.* (191), the amount of heparin in normal blood is very small. The finding of Horn & Borsodi (192) and Koller (193) that the antithrombin potency of serum or plasma is diminished when toluidine blue is added suggests blood contains some heparin. According to Koller and also Grunke (194), the antithrombic titer increases in various diseases, particularly of the liver. Mihalyi's finding (195) that bile salts have an inhibitory action on fibrinogen may perhaps explain in part these findings. Horn & Borsodi conclude that some of the heparin of the plasma is bound because heparin activity increases on standing. Tanturi & Wetzel (196) consider heparin the normal anticoagulant of plasma, because protamine sulfate reduces the antithrombin activity of fresh normal oxalated plasma to a fixed minimum.

Jorpes (197) reported further chemical studies on heparin and pointed out the difficulty of obtaining a chemically pure product. Jensen *et al.* (198) found by electrophoresis that commercial heparins are not homogeneous. A new method for extracting heparin with potassium thiocyanate was outlined by Snellman *et al.* (199).

Methods for studying and determining heparin were described by Astrup (200), DeBeer (201), Foster (202), Mangieri (203), Monkhouse *et al.* (191), Quivy (204, 205), and Kjems (206). The occurrence of mast cell tumors rich in heparin were reported both in man (207) and animals (208).

It is generally recognized that heparin potentiates the antithrombic activity of a substance present in the serum albumin fraction. Holden *et al.* (209) have found that hypoalbuminemic plasma may show a reduced cofactor activity. The response of the clotting time to standardized injections of heparin, the heparin tolerance test, is likely influenced by this cofactor. Whether patients with thromboembolic disease who show hypoactivity to heparin, according to Hagedorn & Barker (210), and Tuft & Rosenfield (211), lack cofactor has not been established. Jaques & Ricker (212) point out that such tests also measure the speed with which heparin is removed from circulation.

Allen, Jacobson, and their associates (213 to 217) have devised a protamine titration test which consists in determining how much protamine is required to counteract the anticoagulant action of a standard quantity of heparin added to blood. They find that the protamine titration is increased after irradiations and in various bleeding diseases. They do not believe that this increase is caused by heparin, but by a heparinoid substance. Some of the bleeding conditions in which the heparinoid activity is increased respond therapeutically to toluidine blue and to protamine. Conley *et al.* (190), who observed that the concentration of heparin required to inhibit clotting is directly related to the platelet count, question the significance of the heparin tolerance tests; but Allen (214) answers their objections.

Miscellaneous anticoagulants continue to be reported. Zierler *et al.* (217a) found that  $\alpha$ -tocopheryl phosphate is antithrombic. Kazal *et al.* (218) reported the isolation of a crystalline trypsin inhibitor from pancreas that is antithrombic. Fisch & Towbin (219) prepared a substance from testicular tissue which has antithromboplastic action. The results of Shinowara's studies (220) indicate that purified fibrinogen may still contain heparin cofactor. According to Menghini (221) penicillin behaves as an anticoagulant, whereas Macht (222) attributes thromboplastic activity to this agent.

## FIBRINOGEN

*Function and structure.*—Fibrinogen is generally considered a passive factor in coagulation, although Fiehrer (223) has expressed his belief that the fibriles of fibrin in hemophilia are not normal in their adsorption of thrombin and fibrinolysin. In the conversion of fibrinogen to fibrin, Laki (224) postulated that thrombin activates the molecule which then polymerizes to form fibrin. These two steps can be separated, and this leads to the concept that two forms of fibrinogen exist. Horanyl (225) has reported experiments in which a labile and a stable form can be separated. According to Laki (226) and Mihalyi *et al.* (227) the polymerization is through amino or phenolic groups. The latter authors make comparisons between the coagulation of fibrinogen with formaldehyde and quinone to that with thrombin. Bagdy *et al.* (228) presented evidence that the sulfhydryl groups are not involved: tests for free sulfhydryl groups are negative, and fibrinogen, treated with agents such as potassium ferricyanide which oxidize sulfhydryl groups still clots. These findings do not agree with Lyons' hypothesis that the conversion of normal fibrinogen to fibrinogen B is brought about by liberation of free sulfhydryl groups. Cummine & Lyons (229) described a simple test for detecting fibrinogen B in plasma. This form may occur in circulating blood and be a factor in thrombosis.

Edsall *et al.* (230) reported further physicochemical studies on fibrinogen and found that the molecule is probably an ellipsoid 700 Å long with an axial ratio of 18 to 1. Hawn & Porter (231) by means of the electronmicroscope found that the fibers of fibrin possess cross striations of constant periodicity. Similar studies were reported by Hall (232, 233). Ware *et al.* (234) described a new method for preparing pure fibrinogen depending on its flocculation when frozen plasma is thawed. The fibrin from this product possesses good tensile strength which is increased by calcium. They, as well as Lorand (235), confirm Robbins' observation that calcium decreases the solubility of fibrin. Morrison (236) has studied the factors that influence the accuracy of the determination of fibrinogen and found that occlusion of other proteins may introduce serious errors.

*Fibrinolysin.*—Mole (237) and Macfarlane & Biggs (238) review recent concepts of fibrinolysin. According to Mole, the enzyme which acts specifically on fibrin, and not on fibrinogen, appears as the result of the body's reaction to injury. Endothelial

lining is concerned in its formation, and it is normally present in cadaver blood except when death is due to infection or cachexia. Macfarlane & Biggs hold that it occurs in conditions in which epinephrine is secreted and that it is intimately related with coagulation, while Halse (239) believes the two processes are distinct. Ratnoff (240) found that the fibrinolysin obtained by activation with streptokinase appeared identical with the product obtained by the action of chloroform. Fantl & Simon (241) observed that electrically induced convulsions cause transient fibrinolytic activity. Astrup & Permin (242) reported that the activator can be prepared from various animal tissues.

Loomis *et al.* (243) have concentrated the antifibrinolysin and have defined the unit. They found that their product has no effect on coagulation. Guest *et al.* found that this agent is increased in chick macrocytic anemia (244), in pernicious anemia, and several other diseases, but not in hemophilia or purpura (245). These authors (246) discussed various factors to be considered in the assay of antifibrinolysin and reported the relative concentrations in various species. Much important work has been reported on streptokinase and bacterial coagulase, which cannot be presented because of lack of space.

#### MISCELLANEOUS

*Tests.*—The coagulation test was studied by Quick *et al.* (68), who stress its limitations and offer specific recommendations for its standardization. Kadish (247) found no direct relationship between clotting time in lusteroid tubes and prothrombin level after dicumarol. Instruments for measuring clotting have been described by Rosenbaum & Barker (248), Wiener & Shapiro (249), Hartert (250), and Voorhees *et al.* (251). Rosenthal & Tobias (252) have developed an instrument for measuring electrical resistance of blood and have applied it to study cell volume and clotting time and retraction. Copley (253) devised an apparatus for controlled negative pressure to test capillary resistance. Roskam *et al.* (254), on the basis of clinical observations, pointed out the inconstancy of the capillary fragility or tourniquet test. Jubelirer & Glueck (255) found no relation between capillary fragility and bleeding due to dicumarol. Duesberg (256) reported an extended study of the bleeding time.

*Reviews.*—Many valuable reviews have appeared: Seegers &

Sharp (257) on hemostatic agents; Glavind (258) on coagulation of crustacean blood; Macfarlane (259), Arvy (260), and Fredericq (261) on coagulation; Favre-Gilly (262) on fibrinopenia; Barthe (263) on hypoprothrombinemia; Milhet (264) on thromboplastin; and Gairdner (265) on Schönlein-Henoch purpura. Particularly recommendable is the report of the First Conference on blood clotting, sponsored by the Macy Foundation (266), in which several major topics are presented and discussed by a group of men who are active workers in the field. It is regrettable that lack of space prevented reviewing the advances in hemophilia, purpura, thrombosis, rutin, and allied subjects.

## LITERATURE CITED

1. CHEN, T. I., AND TSAI, C., *J. Physiol. (London)*, **107**, 280-88 (1948)
2. HUMBLE, J. G., *Blood*, **4**, 69-75 (1949)
3. LAUFMAN, H., MARTIN, W. B., AND TUELL, S. W., *Surg. Gynecol. Obstet.*, **87**, 641 (1948)
4. ZUCKER, M. B., *Am. J. Physiol.*, **148**, 275-88 (1947)
5. BRUN, G. C., *Acta Pharmacol. Toxicol.*, **4**, 251-64 (1948)
6. BRUN, G. C., *Acta Pharmacol. Toxicol.*, **5**, 53-74 (1949)
7. RAPPORT, M. M., GREEN, A. A., AND PAGE, I. H., *Science*, **108**, 329-30 (1948)
8. RAPPORT, M. M., GREEN, A. A., AND PAGE, I. H., *J. Biol. Chem.*, **174**, 735-41 (1948)
9. RAPPORT, M. M., GREEN, A. A., AND PAGE, I. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 582-84 (1948)
10. MILSTONE, J. H., *J. Gen. Physiol.*, **31**, 301 (1948)
11. MILSTONE, J. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 225-28 (1948)
12. CONLEY, C. L., HARTMANN, R. C., AND MORSE, W. I., *J. Clin. Invest.*, **28**, 340-52 (1949)
13. BRINKHOUS, K. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 117-20 (1947)
14. QUICK, A. J., *Federation Proc.*, **6**, 284 (1947)
15. PATTON, T. B., WARE, A. G., AND SEEGER, W. H., *Blood*, **3**, 656-59 (1946)
16. WARE, A. G., FAHEY, J. L., AND SEEGER, W. H., *Am. J. Physiol.*, **154**, 140-47 (1948)
17. QUICK, A. J., SHANBERGE, J. N., AND STEFANINI, M., *Am. J. Med. Sci.*, **217**, 198-205 (1949)
18. QUICK, A. J., *Marquette Med Rev.*, **13**, 89-94 (1948)
19. QUICK, A. J., *Am. J. Med. Sci.*, **214**, 272-80 (1947)
20. QUICK, A. J., AND FAVRE-GILLY, J., *Am. J. Physiol.*, **58**, 387-95 (1949)
21. ZATTI, P., *Boll. soc. ital. biol. sper.*, **24**, 22-31 (1948)
22. WARE, A. G., GUEST, M. M., AND SEEGER, W. H., *Science*, **106**, 41 (1947)
23. WARE, A. G., MURPHY, R. C., AND SEEGER, W. H., *Science*, **106**, 618 (1947)
24. MURPHY, R. C., WARE, A. G., AND SEEGER, W. H., *Am. J. Physiol.*, **151**, 338-41 (1947)
25. WARE, A. G., AND SEEGER, W. H., *J. Biol. Chem.*, **172**, 699-705 (1948)
26. WARE, A. G., AND SEEGER, W. H., *Am. J. Physiol.*, **152**, 567-76 (1948)
27. SYKES, E. M., SEEGER, W. H., AND WARE, A. G., *Proc. Soc. Exptl. Biol. Med.*, **67**, 506-7 (1948)
28. WARE, A. G., AND SEEGER, W. H., *J. Biol. Chem.*, **174**, 565-75 (1948)
29. SEEGER, W. H., AND WARE, A. G., *Federation Proc.*, **8**, 249 (1949)
30. FAHEY, J. L., WARE, A. G., AND SEEGER, W. H., *Am. J. Physiol.*, **154**, 122-33 (1948)
31. QUICK, A. J., AND STEFANINI, M., *J. Gen. Physiol.*, **32**, 191-202 (1948)
32. HONORATO, R., ROJAS, C., AND IVANOVIC, N., *Proc. Soc. Exptl. Biol. Med.*, **68**, 300-1 (1948)
33. MURPHY, R. C., AND SEEGER, W. H., *Am. J. Physiol.*, **154**, 134-39 (1948)
34. STEFANINI, M., AND QUICK, A. J., *Federation Proc.*, **7**, 191-2 (1947)
35. QUICK, A. J., AND STEFANINI, M., *J. Lab. Clin. Med.*, **33**, 819-26 (1948)

36. FANTL, P., AND EVERARD, B. A., *Australian J. Exptl. Biol. Med. Sci.*, **27**, 197-205 (1949)
37. MURPHY, R. C., WARE, A. G., AND SEEGER, W. H., *Proc. Soc. Exptl. Biol. Med.*, **69**, 216-17 (1948)
38. ALEXANDER, B., AND DE VRIES, A., *J. Clin. Invest.*, **28**, 24-31 (1949)
39. HONORATO, R., AND QUICK, A. J., *Am. J. Physiol.*, **140**, 405-8 (1947)
40. FANTL, P., AND NANCE, M. H., *Australian J. Exptl. Biol. Med. Sci.*, **26**, 207-13 (1948)
41. HONORATO, R., *Am. J. Physiol.*, **150**, 381-88 (1947)
42. STEFANINI, M., *Am. J. Clin. Path.*, **18**, 537-41 (1948)
43. MUNRO, M. P., AND MUNRO, F. L., *Am. J. Physiol.*, **150**, 409-14 (1947)
44. FAVRE-GILLY, J., *Rev. d'hématologie*, **4**, 70-94 (1948)
45. OWREN, P. A., *Biochem. J.*, **43**, 136-39 (1948)
46. FANTL, P., AND NANCE, M. H., *Med. J. Australia*, **1**, 128-33 (1948)
47. QUICK, A. J., AND STEFANINI, M., *J. Lab. Clin. Med.*, **34**, 973-82 (1949)
48. LEWIS, J. H., AND FERGUSON, J. H., *J. Clin. Invest.*, **27**, 778-84 (1948)
49. QUICK, A. J., AND STEFANINI, M., *J. Lab. Clin. Med.*, **34**, 1203-15 (1949)
50. ALEXANDER, B., DE VRIES, A., GOLDSTEIN, R., AND LANDWEHR, G., *Science*, **109**, 545 (1949)
51. DE VRIES, A., ALEXANDER, B., AND GOLDSTEIN, R., *Blood*, **4**, 247-58 (1947)
52. ALEXANDER, B., DE VRIES, A., AND GOLDSTEIN, R., *Blood*, **4**, 739-47 (1949)
53. ALEXANDER, B., AND DE VRIES, A., *Blood*, **4**, 747-52 (1949)
54. ALEXANDER, B., AND DE VRIES, A., *Blood*, **4**, 752-58 (1949)
55. JACOX, R. F., AND BAYS, R. P., *Proc. Soc. Exptl. Biol. Med.*, **70**, 587-89 (1949)
56. JACOX, R. F., *J. Clin. Invest.*, **28**, 492-504 (1949)
57. MANN, F. D., HURN, M., AND MAGATH, T. B., *Proc. Soc. Exptl. Biol. Med.*, **6**, 33-35 (1947)
58. MANN, F. D., AND HURN, M., *Proc. Soc. Exptl. Biol. Med.*, **67**, 83-85 (1948)
59. FRICK, P., *Helv. Med. Acta*, **15**, 614-32 (1948)
60. KOLLER, F., AND FRICK, P., *Helv. Chim. Acta*, **23**, 717-22 (1949)
61. ALEXANDER, B., DE VRIES, A., AND GOLDSTEIN, R., *New Engl. J. Med.*, **240**, 403-12 (1949)
62. CONLEY, C. L., AND MORSE, W. I., *Am. J. Med. Sci.*, **215**, 158-69 (1948)
63. HURN, M., BARKER, N. W., AND MANN, F. D., *Am. J. Clin. Path.*, **17**, 709-11 (1947)
64. FISHER, B., *Am. J. Med. Sci.*, **215**, 39-41 (1948)
65. UNGER, P. N., AND SHAPIRO, S., *Blood*, **3**, 137-46 (1948)
66. UNGER, P. N., AND SHAPIRO, S., *J. Clin. Invest.*, **27**, 39-47 (1948)
67. WARE, A. G., AND SEEGER, W. H., *Am. J. Clin. Path.*, **19**, 471-82 (1949)
68. QUICK, A. J., HONORATO, R., AND STEFANINI, M., *Blood*, **3**, 1120-29 (1948)
69. QUICK, A. J., *Lancet*, **II**, 379-82 (1947)
70. QUICK, A. J., *Am. J. Physiol.*, **151**, 63-70 (1947)
71. HURN, M., BARKER, N. W., AND MANN, F. D., *Am. J. Clin. Path.*, **17**, 712-18 (1947)
72. OWEN, C. A., AND BOLLMAN, J. L., *Proc. Soc. Exptl. Biol. Med.*, **67**, 231-34 (1948)
73. MAWSON, C. A., *J. Lab. Clin. Med.*, **34**, 458-72 (1949)
74. WILSON, S., *Proc. Soc. Exptl. Biol. Med.*, **66**, 126-28 (1947)

75. CHENEY, G., *Stanford Med. Bull.*, **5**, 175-81 (1947)
76. LEMPERT, H., *Brit. Med. J.*, **1**, 125 (1948)
77. BIGGS, R., AND MACFARLANE, R. G., *K. Clin. Path.*, **2**, 33-44 (1949)
78. JAMES, G. A., *J. Clin. Path.*, **2**, 45-48 (1949)
79. OLWIN, J. H., *Am. J. Med. Sci.*, **217**, 427-37 (1949)
80. OLWIN, J. H., *J. Lab. Clin. Med.*, **34**, 806-13 (1949)
81. HURN, M., AND MANN, F. D., *Am. J. Clin. Path.*, **17**, 741-46 (1947)
82. DUFF, I. F., AND SHULL, W. H., *J. Am. Med. Assoc.*, **139**, 762-65 (1949)
83. MANN, F. D., BUTT, H. R., AND HURN, M., *Gastroenterology*, **11**, 221-26 (1948)
84. DAM, H., *Nature*, **161**, 1010-11 (1948)
85. DAM, H., AND SONDERGAARD, E., *Biochem. et Biophys. Acta*, **2**, 409-13 (1948)
86. FAHEY, J. L., OLWIN, J. H., AND WARE, A. G., *Proc. Soc. Exptl. Biol. Med.*, **69**, 491-94 (1948)
87. LEIN, J., AND LEIN, P. S., *Am. J. Physiol.*, **155**, 394-401 (1948),
88. MACMILLAN, R. L., *Science*, **108**, 416-17 (1948)
89. JAMES, D., BUTLER, J. J., BENNETT, I. L., AND SCHEINBERG, P., *J. Clin. Invest.*, **27**, 541 (1948)
90. JAMES, D. F., BENNETT, I. L., SCHEINBERG, P., AND BUTLER, J. J., *Arch. Internal Med.*, **83**, 632-51 (1949)
91. QUICK, A. J., AND STEFANINI, M., *J. Biol. Chem.*, **175**, 945-52 (1948)
92. BOYD, E. J., AND WARNER, E. D., *J. Lab. Clin. Med.*, **33**, 1431-37 (1948)
93. MARTIN, G. J., AND SWAYNE, V., *Science*, **109**, 201-2 (1949)
94. JÜRGENS, R., *Z. Vitaminforsch.*, **19**, 342-61 (1948)
95. GALEONE, A., AND ROMAGNOLO, A., *Minerva med.*, **1**, 169-73 (1948)
96. DAVIES, C. W., *Brit. Med. J.*, **II**, 943 (1948)
97. THORSEN, G., *Lancet*, **II**, 420-22 (1947)
98. KRAUS, A. P., PERLOW, S., AND SINGER, K., *J. Am. Med. Assoc.*, **139**, 758-61 (1949)
99. SACHS, J. J., AND LABATE, J. S., *Am. J. Obstet. Gynecol.*, **57**, 965-71 (1949)
100. AXTRUP, S., *Acta Paediat.*, **35**, 351-54 (1948)
101. LEWITUS, Z. A., *Arch. Internal Med.*, **82**, 625 (1948)
102. BLOOD, D. W., AND PATTERSON, M. C., *Proc. Soc. Exptl. Biol. Med.*, **69**, 130-33 (1948)
103. HOLLAND, H., AND GROSS, E. G., *J. Iowa State Med. Soc.*, **38**, 183 (1948)
104. MCCORMICK, H. M., AND YOUNG, I. I., *Proc. Soc. Exptl. Biol. Med.*, **70**, 501-3 (1949)
105. HONORATO, R., AND LOPETEGUI, M., *Rev. soc. argentina biol.*, **24**, 286-94 (1948)
106. MUSHETT, C. W., AND SEELER, A. O., *J. Pharmacol. Exptl. Therap.*, **91**, 84-91 (1947)
107. FANTL, P., AND NANCE, M. H., *Med. J. Australia*, **II**, 133-36 (1947)
108. KAULLA, K. N. v., AND PULVER, R., *Schweiz. med. Wochschr.*, **78**, 806-10 (1948)
109. PULVER, R., AND KAULLA, K. N. v., *Schweiz. med. Wochschr.*, **78**, 956-50 (1948)
110. REINIS, Z., AND KUBIK, M., *Schweiz. med. Wochschr.*, **78**, 785-90 (1948)
111. DE NICOLA, P., *Farm. sci. e tec.*, **4**, 152-60 (1949)
112. DE NICOLA, P., *Boll. ist. sieroterap. milan.*, **27**, 180-89 (1948)

113. SOULIER, J. P., AND GUEGUEN, J., *Rev. d'hématologie*, **3**, 180-84 (1948)
114. JAKES, L. B., TAYLOR, E., AND LEPP, E., *Federation Proc.*, **8**, 81 (1949)
115. SELANDER, P., AND BERNIUS, B., *Ann. Paediat.*, **169**, 404-6 (1947)
116. JAKES, L. B., AND LEPP, E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 178-81 (1947)
117. MADDOCK, C. L., WOLBACH, S. B., AND JENSEN, D., *Federation Proc.*, **7**, 275 (1948)
118. WALKER, S. E., EYLENBURG, E., AND MOORE, T., *Biochem. J.*, **41**, 575-80 (1947)
119. MANN, J. D., MANN, F. D., AND BOLLMAN, J. L., *Federation Proc.*, **8**, 362 (1949)
120. BRAGANCA, B. DE M., AND RADHAKRISHNA, M. V. R., *Indian J. Med. Research*, **35**, 15-21 (1947)
121. FIELD, J. B., *Cancer Research*, **8**, 172-76 (1948)
122. VAN DEN, OSTENDE, M. J., *Fynaecologia*, **127**, 110-14 (1949),
123. DOLES, H. M., *Southern Med. J.*, **40**, 965-73 (1947)
124. GLAVIND, J., GRANADOS, H., HANSEN, L. A., SCHILLING, K., KRUSE, I., AND DAM, H., *Rev. intern. Vitaminologie*, **20**, 234-38 (1948)
125. DAM, H., HJORTH, E., AND KRUSE, I., *Physiol. Plantarum*, **1**, 379-81 (1948)
126. HEINDL, I. A., ANDERSON, B. G., AND FRIEDLANDER, R. D., *Ann. Internal Med.*, **29**, 347-56 (1948)
127. HAGEN, P. S., AND WATSON, C. J., *J. Lab. Clin. Med.*, **33**, 542-54 (1948)
128. RANDALL, A., AND RANDALL, J. P., *Proc. Soc. Exptl. Biol. Med.*, **70**, 215-18 (1949)
129. QUICK, A. J., *Science*, **106**, 591 (1947)
130. STEFANINI, M., AND QUICK, A. J., *Am. J. Physiol.*, **152**, 389-96 (1948)
131. STEFANINI, M., *Proc. Soc. Exptl. Biol. Med.*, **67**, 22-25 (1948)
132. HARGREAVES, B., *Rev. brasil. biol.*, **7**, 311-21 (1947)
133. SEEGER, W. H., AND WARE, A. G., *Federation Proc.*, **7**, 186-87 (1948)
134. GERENDAS, M., *Hung. Acta Physiol.*, **1**, 97-115 (1948)
135. JÜRGENS, R., AND STUDER, A., *Helv. Physiol. et Pharmacol. Acta*, **6**, 130-49 (1948)
136. QUICK, A. J., AND STEFANINI, M., *Proc. Soc. Exptl. Biol. Med.*, **67**, 111-12 (1948)
137. CRADDOCK, C. G., JR., AND LAWRENCE, J. S., *Blood*, **2**, 505-18 (1947)
138. SOULIER, J. P., AND BURSTEIN, M., *Blood*, **3**, 1188-96 (1948)
139. CONLEY, C. L., RATHBUN, H., MORSE, W. I., AND ROBINSON, J. E., JR., *Bull Johns Hopkins Hosp.*, **83**, 288-96 (1948)
140. TAGNON, H. J., AND SOULIER, J. P., *Blood*, **3**, 1161-66 (1948)
141. NIKOLAEVA, N. I., *Byull. Eksptl. Biol. Med.*, **22**, 24-27 (1946)
142. FERGUSON, J. H., TRAVIS, B. L., AND GERHEIM, E. B., *Blood*, **3**, 1130-60 (1948)
143. GARCES, B. C., LEYTON, G., AND GARCES, S. M., *Rev. d'hématologie*, **3**, 347-62 (1948)
144. LEIN, J., AND LEIN, P. S., *Proc. Soc. Exptl. Biol. Med.*, **70**, 446-48 (1949)
145. HOLDEN, W. D., COLE, J. W., PORTMANN, A. F., AND STORAASLI, J. P., *Proc. Soc. Exptl. Biol. Med.*, **70**, 553-66 (1949)
146. CHARGAFF, E., *J. Biol. Chem.*, **173**, 253-62 (1948)

147. CHARGAFF, E., AND GREEN, C., *J. Biol. Chem.*, **173**, 263-70 (1948)
148. LEWIS, J. H., AND FERGUSON, J. H., *J. Clin. Invest.*, **27**, 778-84 (1948)
149. TOCANTINS, L. M., CARROLL, R. T., AND MCBRIDGE, T. J., *Proc. Soc. Exptl. Biol. Med.*, **68**, 110-17 (1948)
150. OVERMAN, R. S., AND WRIGHT, I. S., *J. Biol. Chem.*, **174**, 759-60 (1948)
151. QUICK, A. J., AND FAVRE-GILLY, J., *Blood* (In press)
152. SOULIER, J. P., *Rev. d'hématologie*, **3**, 302-19 (1948)
153. SOULIER, J. P., *Sang, Le*, **19**, 78-94 (1948)
154. ALEXANDER, B., DE VRIES, A., AND GOLDSTEIN, R., *J. Clin. Invest.*, **27**, 523 (1948)
155. QUICK, A. J., *Pediatrics*, **3**, 312-17 (1948)
156. QUICK, A. J., SHANBERGE, J. N., AND STEFANINI, M., *J. Lab. Clin. Med.*, **34**, 761-67 (1949)
157. BESSIS, M., AND BURSTEIN, M., *Rev. d'hématologie*, **3**, 48-68 (1948)
158. GUTTMANN, W., *Z. ges. inn. Med.*, **2**, 362-76 (1947)
159. FONIO, A., *Praxis Schweiz. Rundschau Med.*, **43**, 23 (1947)
160. FONIO, A., *Bull. Schweiz. Akad. Med. Wiss.*, **4**, 470-81 (1948),
161. FONIO, A., *Schweiz. med. Wochschr.*, **78**, 973-74 (1948)
162. CHEVALLIER, P., AND FIEHRER, A., *Sang, Le*, **18**, 560-64 (1947)
163. HIRSCHBOECK, J. S., *J. Lab. Clin. Med.*, **33**, 347-55 (1948)
164. CRUZ, W. O., AND DA SILVA, E. M., *Proc. Soc. Exptl. Biol. Med.*, **70**, 210-13 (1949)
165. CARTER, J. R., *Am. J. Med. Sci.*, **213**, 585-92 (1947)
166. FITZGERALD, P. J., AUERBACH, O., AND FRAME, E., *Blood*, **2**, 519-41 (1947)
167. SINGER, K., BORNSTEIN, F. P., AND WILE, S. A., *Blood*, **2**, 542-54 (1947)
168. MUIRHEAD, E. E., CRASS, G., AND HILL, J. M., *Am. J. Clin. Path.*, **18**, 523-32 (1948)
169. MOSCHCOWITZ, E., *Ann. Internal Med.*, **30**, 1156-79 (1949)
170. ACKROYD, J. B., *Clin. Sci.*, **7**, 249-83 (1949)
171. WATSON, C. J., SCHULTZ, A. L., AND WAIKOFF, H. M., *J. Lab. Clin. Med.*, **32**, 606-17 (1947)
172. POHLE, F. J., AND COHEN, E. B., *J. Lab. Clin. Med.*, **32**, 1395-96 (1947)
173. MADISON, F. W., *Blood*, **3**, 1083-89 (1948)
174. COPLEY, A. L., *Federation Proc.*, **7**, 22-23 (1948)
175. COPLEY, A. L., *J. Am. Med. Assoc.*, **137**, 145 (1948)
176. FIDLAR, E., AND JAKUES, L. B., *J. Lab. Clin. Med.*, **33**, 1410-23 (1948)
177. QUICK, A. J., SHANBERGE, J. N., AND STEFANINI, M., *J. Lab. Clin. Med.*, **33**, 1424-30 (1948)
178. FLECK, L., *J. Am. Med. Assoc.*, **139**, 542 (1949),
179. WEINER, M., ZELTMACHER, K., REICH, C., AND SHAPIRO, S., *Blood*, **3**, 1275-82 (1948)
180. MORRISON, M., RICHTER, I. H., AND LOEWE, L., *Am. J. Clin. Path.*, **18**, 879-84 (1948)
181. MOOLTEN, S. E., VROM, L., VROMAN, G. M. S., AND GOODMAN, B., *Arch. Internal Med.* (In press)
182. CRUZ, W. O., AND DA SILVA, E. M., *Brit. J. Pharmacol.*, **4**, 132-34 (1949)
183. TOCANTINS, L. M., *Blood*, **3**, 1073-82 (1948)

184. BURSTEIN, M., AND BESSIS, M., *Rev. d'hématologie*, **3**, 69-91 (1948)
185. CROIZAT, P., FAVRE-GILLY, J., PERRIN, L., AND DURANT, J., *J. Méd. Lyon*, **30**, 83-97 (1949)
186. GERENDAS, M., CSEFKO, I., AND UDVARDY, M. D. F., *Nature*, **162**, 257-58 (1948)
187. BARNARD, R., *Science*, **107**, 571-73 (1948)
188. ASTRUP, P., *Acta Pharmacol. Toxicol.*, **3**, 179-83 (1947)
189. TOCANTINS, L. M., *Blood*, **3**, 1304-5 (1948)
190. CONLEY, C. L., HARTMANN, R. C., AND LALLEY, J. S., *Proc. Soc. Exptl. Biol. Med.*, **69**, 284-87 (1948)
191. MONKHOUSE, F. C., STEWART, M., AND JAKUES, L. B., *Federation Proc.*, **8**, 112 (1949)
192. HORN, Z., AND BORSODI, L., *Schweiz. med. Wochschr.*, **78**, 1069-73 (1948)
193. KOLLER, F., AND FRITSCHY, W., *Helv. Med. Acta.*, **14**, 263 (1947)
194. GRUNKE, W., *Z. ges. inn. Med.*, **3**, 409-15 (1948)
195. MIHALYI, E., *Hung. Acta Physiol.*, **1**, 179-91 (1948)
196. TANTURI, C. A., AND WETZEL, N. C., *Am. J. Med. Sci.*, **217**, 410-20 (1949)
197. JORPES, J. E., AND GARDELL, S., *J. Biol. Chem.*, **176**, 267-76 (1948)
198. JENSEN, R., SNELLMAN, O., AND SYLVIN, B., *J. Biol. Chem.*, **174**, 265-71 (1948)
199. SNELLMAN, O., JENSEN, R., AND STYLES, B., *Nature*, **161**, 639 (1948)
200. ASTRUP, P., *Acta Pharmacol. Toxicol.*, **3**, 165-78 (1947)
201. DE BEER, E. J., *Am. J. Physiol.*, **151**, 59-62 (1947)
202. FOSTER, R. H. K., *Am. J. Physiol.*, **152**, 577-84 (1948)
203. MANGIERI, C. N., *J. Lab. Clin. Med.*, **32**, 901-4 (1947)
204. QUIVY, D., *Compt. rend. soc. biol.*, **141**, 608-11 (1947)
205. QUIVY, D., *Compt. rend. soc. biol.*, **141**, 974-76 (1947)
206. KJEMS, H., AND WAGNER, H., *Acta Pharmacol. Toxicol.*, **4**, 155-63 (1948)
207. EHRRICH, W. E., SEIFTER, J., ALBURN, H. E., AND BEGANY, A. J., *Proc. Soc. Exptl. Biol. Med.*, **70**, 183-84 (1949)
208. OLIVER, J., BLOOM, F., AND MANGIERI, C., *J. Exptl. Med.*, **86**, 107-16 (1947)
209. HOLDEN, W. D., COLE, J. W., AND DAVIS, J. R., *Surg. Gynecol. Obstet.*, **89**, 20-23 (1949)
210. HAGEDORN, A. B., AND BARKER, N. W., *Am. Heart J.*, **35**, 603-10 (1948)
211. TUFT, H. S., AND ROSENFELD, R. E., *Am. J. Clin. Path.*, **17**, 682-65 (1947)
212. JAKUES, L. B., AND RICKER, A. G., *Blood*, **3**, 1197-1212 (1948)
213. ALLEN, J. G., SANDERSON, M., MILHAM, H., AND JACOBSON, L. O., *J. Exptl. Med.*, **87**, 71-86 (1948)
214. ALLEN, J. G., MOULDER, P. V., MCKEEN, C. L., EGNER, W., ELGHAMMER, R. M., AND GROSSMAN, B. J., *Proc. Soc. Exptl. Biol. Med.*, **70**, 244-46 (1949)
215. ALLEN, J. G., GROSSMAN, B. J., ELGHAMMER, R. M., MOULDER, P. V., MCKEEN, C. L., JACOBSON, L. O., PIERCE, M., SMITH, T. R., AND CROSBIE, J. M., *J. Am. Med. Assoc.*, **139**, 125-54 (1949)
216. ALLEN, J. G., MOULDER, P. V., ELGHAMMER, R. M., GROSSMAN, B. J., MCKEEN, C. L., SANDERSON, M., EGNER, W., AND CROSBIE, J. M., *J. Lab. Clin. Med.*, **34**, 473-81 (1949)
217. JACOBSON, L. O., MARKS, E. K., GASTON, E., ALLEN, J. G., AND BLOCK, M. H., *J. Lab. Clin. Med.*, **33**, 1566-78 (1948)

- 217a. ZIERLER, K. L., GROB, D., AND LILIENTHAL, J. L., *Am. J. Physiol.*, **153**, 127-32 (1948)
218. KAZAL, L. A., SPICER, D. S., AND BRAHINSKY, R. A., *J. Am. Chem. Soc.*, **70**, 3034-40 (1948)
219. FISCH, S., AND TOWBIN, E. J., *Federation Proc.*, **8**, 45 (1949)
220. SHINOWARA, G. Y., *Am. J. Physiol.*, **156**, 458-64 (1949)
221. MENGHINI, G., *Boll. soc. ital. biol. sper.*, **24**, 720-21 (1948)
222. MACHT, D. I., *Southern Med. J.*, **41**, 720-27 (1948)
223. FIEHRER, A., *Sang, Le*, **20**, 248-52 (1949)
224. LAKI, L., *Federation Proc.*, **8**, 90 (1949)
225. HORANYL, M., *Acta Med. Scand.*, **133**, 210-13 (1949)
226. LAKI, K., AND MIHALYI, E., *Nature*, **163**, 66 (1949)
227. MIHALYI, E., AND LORAND, L., *Hung. Acta Physiol.*, **1**, pp. 218-39 (1948)
228. BAGDY, D., GUBA, F., LORAND, L., AND MIHALYI, E., *Hung. Acta Physiol.*, **1**, 197-211 (1948)
229. CUMMINE, H., AND LYONS, R. N., *Brit. J. Surg.*, **35**, 339-63 (1948)
230. EDSALL, J. T., FOSTER, J. F., AND SCHEINBERG, H., *J. Am. Chem. Soc.*, **69**, 2731-38 (1948)
231. HAWN, C. VAN Z., AND PORTER, K. R., *J. Exptl. Med.*, **86**, 285-92 (1947)
232. HALL, C. E., *J. Biol. Chem.*, **179**, 857-64 (1949)
233. HALL, C. E., *J. Am. Chem. Soc.*, **71**, 1138-39 (1949)
234. WARE, A. G., GUEST, M. M., AND SEEGER, W. H., *Arch. Biochem.*, **13**, 231-36 (1947)
235. LORAND, L., *Hung. Acta Physiol.*, **1** (1948)
236. MORRISON, P. R., *J. Am. Chem. Soc.*, **69**, 2723-31 (1947)
237. MOLE, R. H., *J. Path. Bact.*, **60**, 413-27 (1948)
238. MACFARLANE, R. G., AND BIGGS, R., *Blood*, **3**, 1167-87 (1948)
239. HALSE, T., *Deut. med. Wochschr.*, **72**, 81-83 (1947)
249. RATNOFF, O. D., *J. Exptl. Med.*, **87**, 199-228 (1948)
241. FANTL, P., AND SIMON, S. E., *Australian J. Exptl. Biol. Med. Sci.*, **26**, 53-29 (1948)
242. ASTRUP, T., AND PERMIN, P. M., *Nature*, **161**, 689-90 (1948)
243. LOOMIS, E. C., RYDER, A., AND GEORGE, C., *Arch. Biochem.*, **20**, 446-50 (1949)
244. GUEST, M. M., WARE, A. G., AND SEEGER, W. H., *Am. J. Physiol.*, **150**, 661-69 (1947)
245. GUEST, M. M., DALY, B. M., WARE, A. G., AND SEEGER, W. H., *J. Clin. Invest.*, **27**, 793-94 (1948)
246. GUEST, M. M., DALY, B. M., BYRNE, M., WARE, A. G., AND SEEGER, W. H., *J. Clin. Invest.*, **27**, 785-91 (1948)
247. KADISH, A. H., *Am. Heart J.*, **34**, 225-29 (1947)
248. ROSENBAUM, E. E., AND BARKER, N. W., *J. Lab. Clin. Med.*, **33**, 1342-47 (1948)
249. WIENER, M. J., AND SHAPIRO, S., *J. Lab. Clin. Med.*, **32**, 1037-41 (1947)
250. HARTERT, H., *Klin. Wochschr.*, **26**, 577-83 (1948)
251. VOORHEES, A. B., GRAFF, S., AND BLAKEMORE, A. N., *J. Lab. Clin. Med.*, **34**, 133-39 (1949)

252. ROSENTHAL, R. L., AND TOBIAS, C. W., *J. Lab. Clin. Med.*, **33**, 1110-22 (1948)
253. COPLEY, A. L., *Science*, **107**, 201-2 (1948)
254. ROSKAM, J., RENARD, C., AND SWALUE, L., *Blood*, **3**, 1112-19 (1948)
255. JUBELIRER, R. A., AND GLUECK, H. I., *J. Lab. Clin. Med.*, **35**, 448-57 (1949)
256. DUESBERG, J. P., *Rev. belge path. et méd.*, **18**, 33-76 (1947)
257. SEEGER, W. H., AND SHARP, E. A., *Hemostatic Agents*, 131 pp. (C. C Thomas, Springfield, Illinois, 1948)
258. GLAVIND, J., *Studies on the Coagulation of Crustacean Blood*, 137 pp. (Nyt Nordis, Forlag, Kjobenhavn, 1948)
259. MACFARLANE, R. G., *J. Clin. Path.*, **1**, 113-43 (1948)
260. ARVY, L., *J. physiol.*, **39**, 263-320 (1947)
261. FREDERICQ, P., *Données Récentes sur la Coagulation du Sang*, 62 pp. (Masson & Cie, Paris, 1946)
262. FAVRE-GILLY, J., *Les Etats Hémorragiques et la Notion de Fibrinoptie*, 304 pp. (Vigot Frères, Paris, 1947)
263. BARTHE, C., *Contribution à l'Étude des Hypoprothrombinemies Hémorrhagiques*, 132 pp. (Camille Annequin, Lyon, 1948)
264. MILHET, M.-F., *La Thromboplastine et ses Troubles Applications au Diagnostic et au Traitement Actuels de L'Hémophilie*, 184 pp. (Camille Annequin, Lyon, 1949)
265. GAIRDNER, D., *Quart. J. Med.*, **17**, 95-122 (1948)
266. FLYNN, J. E. (Ed.), *Blood Clotting and Allied Problems*, 179 pp. (Josiah Macy Jr. Foundation, New York, 1948)
267. OWREN, P. A., *Lancet*, **I**, 446-48 (1947)

## BLOOD GAS TRANSPORT<sup>1</sup>

BY ROBERT C. DARLING

*Department of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.*

The past three years have been a time of gradual advance in our knowledge of blood gas transport, highlighted by frequent attempts to integrate the available knowledge and often aided by new, precise, and facile techniques. The main part of this review is organized into three sections dealing with three stages in the transport of normal respiratory gases: (a) the equilibrium at the lung barrier, (b) the properties of blood as a carrier of gases, and (c) gas exchange in tissues. Next will follow a summary of reports on the effects of various modifying stresses such as carbon monoxide, high altitude, etc. Finally, there will be a mention of developments in techniques and analytic methods. The subject of pulmonary regulation by blood gases has been largely omitted since it falls more logically in the chapter on the Respiratory System.

*Alveolar-arterial equilibrium.*—The concept of alveolar air as the hypothetical air in effective equilibrium with arterial blood, rather than any particular sample of air, has been proposed and measured by Riley *et al.* (1). Galdson & Wollack (2) checked the method satisfactorily against orthodox alveolar samples in normal individuals. The virtue of the method and concept lies in the rather precise deductions possible regarding the oxygen gradient across the lungs under various conditions. Lilienthal *et al.* (3) have deduced from the well established properties of hemoglobin that the gradient while breathing air at sea level is a function chiefly of "venous admixture," whereas that while breathing gas of low  $pO_2$  is a true membrane gradient. Dirken & Heemstra (4) report similar mathematical deductions. Malmström (5) confirmed the slight increase in gradient during exercise. The method has been profitably applied by Riley *et al.* (6, 7, 8) in the study of pulmonary disease where older methods of alveolar studies were almost useless. Although satisfactory to many workers, the aerotonometer measurement of blood gas tensions, which is essential in the method, has been reported unreliable by Roos & Black (9).

<sup>1</sup> This review covers the period from approximately June 1946 to June 1949.

More orthodox measurements of alveolar gas continue to give instructive results. A continuous alveolar gas analyzer, reported by Rahn *et al.* (10), although giving results (on end expiratory samples) several mm. Hg in  $p\text{CO}_2$  away from arterial analyses, is valuable to show changes during work, anoxia, hyper-, and hypoventilation (11, 12) and has furnished the data for a general graphical and mathematical presentation of the variations in alveolar air (13, 14). The fact that the alveolar gas composition, not that of the inspired gas, determines the degree of oxygen saturation of the blood is further emphasized in the studies of Penneys & Thomas (15) on oximeter control to obtain standard anoxia, in the work of Christensen *et al.* (16) on oxygen therapy, and in the report of Consolazio *et al.* (17) on exposure to high carbon dioxide and low oxygen for periods up to 72 hr.

A comparison by Barker *et al.* (18) of alveolar gas measurements by five methods strengthens the validity of the Riley technique and points out again the small errors in end expiratory samples. An ingenious new technique of sucking out alveolar samples at any phase of respiration and independent of the subject's cooperation was reported by Lambie & Morrissey (19). Contrary to usual assumptions, some gas exchange may occur in the supraglottal dead space according to Galdston & Horwitz (20). The mass spectrograph adapted to continuous alveolar and expired gas analyses by Hitchcock *et al.* (21, 22) is probably the most elegant method for the purpose.

Specific details of the equilibrium between alveolar air and arterial blood while breathing air or higher oxygen concentrations have been reinvestigated because of the inaccuracies of blood measurements in that range. The presence of 1.3 to 3.5 per cent of the hemoglobin in an inactive and partially reversible state in fresh blood was found by Van Slyke *et al.* (23) in partial confirmation of previous reports, although a negligible part of this could be identified as methemoglobin. Among several observers studying arterial blood during oxygen breathing, Fasciolo & Chiodi (24), by measuring the oxygen content and thence the  $p\text{O}_2$  of anaerobically separated plasma, found an alveolar-arterial gradient during breathing of oxygen of only 36 mm. Hg, which corresponds to a maximum "arteriovenous shunt" of 1.6 per cent. By comparing alveolar and arterial values while breathing three concentrations

of oxygen, Lambertson *et al.* (25) concluded that the "shunt" was less than one per cent. Using *in vivo* saturation with oxygen as a measure of capacity, both Comroe & Walker (26) and Wood (27) found arterial oxygen saturations above 97 per cent on breathing air. Using conventional tonometer techniques, Preston & Ordway (28) found the arterial oxygen saturation breathing oxygen to be five per cent too low, thus indirectly confirming the errors of *in vitro* saturation. The principle of *in vivo* equilibration of blood has been extended by Riley *et al.* (29) to include a wide variety of gas mixtures; the oxygen dissociation curve thus obtained agreed with the standard *in vitro* curve. Corollary to this subject is the finding of Dexter *et al.* (30) that "pulmonary capillary" blood, obtained by retrograde flow through a catheter wedged in a small pulmonary artery, was 95 to 98 per cent saturated with oxygen, even in patients with cyanotic congenital heart disease.

The use of the Milliken-type oximeter to follow the changing equilibrium between air and oxygen was another approach to the problem, not wholly clear in its significance, however. Douglas & Edholm (31), Wood *et al.* (32), and Fowler & Comroe (33) found similar time relationships, but somewhat variable responses to 40 per cent oxygen.

*Properties of the blood concerned in gas transport.*—This portion of the review will be restricted to those properties of blood and hemoglobin which bear directly on gas transport. The reader might well refer to the recent excellent reviews of Pauling (34), Wyman (35), and Granick (36) for the relationship of chemical structure to respiratory function in hemoglobin. The physiologic properties also have been reviewed by Barcroft (37).

Standards for measurement of hemoglobin have often been less than ideal. The coordinated analytic team of King *et al.* (38) thoroughly crosschecked the gasometric, colorimetric, and iron methods and reported the limitations of each. When total hemoglobin pigment was determined (to include inactive and carboxy-hemoglobin), this gasometric method agreed well with the hemoglobin measured by iron content. For a colorimetric standard Drabkin (39) proposed cupric ammonium sulfate (for cyanmethemoglobin) and adapted it to routine use in various colorimeters. Holden (40) suggested the advantages of alkaline over acid hematin. The relative accuracy of various colorimetric methods

was carefully determined by MacFarlane *et al.* (41). Vartiainen (42) measured the hemoglobin concentration of packed red cells, with indecisive results.

A valuable tool for the study of the formation and life of the red cell was the basic discovery of Shemin & Rittenberg (43) that glycine (labelled with  $N^{14}$ ) is one of the main building stones of the protoporphyrin of hemoglobin. A normal life span of the red cell of 127 days was measured by this technique (44). In the nucleated red cells of birds (45), and, for some unexplained reason, in the cells of sickle cell disease (46), this synthesis can occur *in vitro*. Another characteristic of sickle cell hemoglobin (abnormal electrophoretic behavior in relation to pH) has been reported by Itano & Pauling (47).

The factors which control hemoglobin concentration continue to be elusive. The oxygen saturation of aspirated bone marrow has been found to deviate from normal neither in induced anemia, according to Grant (48, 49), nor in polycythemia vera, according to Berk *et al.* (50). In fact, with explanted bone marrow Rosin & Rachmilewitz (51) observed damage from oxygen concentrations under 15 per cent, stimulation only from high oxygen concentrations. To explain the stimulus of anoxia on erythropoiesis, Verzar (52) proposed, on the basis of observed initial depression of red count and bilirubinemia in animals at altitude, that bilirubin from hemolysis is the stimulant to the bone marrow. Similarly, in a search for an intermediary stimulant, Klingelhöffer (53) successfully extracted "haemopoietin" (of Carnot & Deflander, 1906) from umbilical cord blood and showed that it is enhanced by exposure to low oxygen and inactivated by high oxygen. Exploring other variables, Post & Spealman (54) were unable to find significant seasonal variations in total hemoglobin; Heath (55) could not relate hemoglobin concentrations in 258 normal young men to any of numerous physiologic and psycho-social measurements.

In recent years, methemoglobin, previously a mere test-tube derivative, has developed physiologic significance. Study of cases of congenital methemoglobinemia by Gibson & Harrison (56) and Eder *et al.* (57) has pointed to an enzymatic defect in the condition. Gibson (58) has established the missing factor as coenzyme factor I, probably the first instance of the proof of a single enzymatic defect as an inborn error of metabolism. The effect of methemoglobin increasing the oxygen affinity of coexist-

ing hemoglobin was confirmed by Gibson & Harrison (59) but not found in Eder's case. Bodansky & Hendley (60) found that, unlike most forms of anoxia, methemoglobinemia does not affect visual thresholds.

The presence of a small amount of methemoglobin in normal blood, always a reasonable assumption but difficult to establish by sufficiently specific methods, was measured as 0.1 gm. per cent by Kiese (61, 62), with a delicate photometric method. The same author (63, 64, 65) studied the substrate factors which normally reduce it. Several of the authors mentioned above, also Bodansky & Gutmann (66), have shown the function of dyes such as methylene blue in reducing methemoglobin by other pathways than the normal enzymatic reduction. The predictable normal disappearance rate of methemoglobin has led Moore *et al.* (67) to use it as a means of tagging injected red cells to measure red cell volume. Whether methemoglobin in normal blood accounts for the difficulties in measuring oxygen equilibrium at high  $pO_2$  is not yet clear. The report of Ramsay (68) on the slow oxygenation of hemoglobin, made faster by previous reduction, falls into the same category.

Investigations on carbonic anhydrase pertinent to this review have been few and scattered. According to Lawrence (69), on the basis of blood measurements of 100 subjects, the enzyme level in the blood is slightly lower in men than women and at its peak in men between the ages of 20 to 25. Makarova (70) could find no variations in respect to feeding in infants. Altschule and colleagues (71, 72, 73), studying anemias, found a good parallelism of the enzyme with blood zinc and red cell mass except for a higher concentration in pernicious anemia and some other chronic anemias. Kreps (74) emphasized variable enzyme inhibitors in the blood in relation to drugs and disease. Torda & Wolff (75) make the interesting recent observation that most of the convulsant drugs are inhibitors of the enzyme and the anti-convulsants are potentiators.

Several other factors affecting the respiratory properties of the blood have been reported. Gordon *et al.* (76) studied systematically the effect of temperature elevation and observed the compensatory influence of respiratory alkalosis occurring in man with fever. According to Morse *et al.* (77) the oxygen dissociation curve in cyanotic congenital heart disease is to the right of normal

and may serve as a beneficial adaptation. Enselman *et al.* (78), studying stored blood, observed a decrease in oxygen affinity before any reduction in oxygen capacity. Cheymol & Henry (79), attempting to explain the anoxic tolerance of young rabbits, found no change in carbon monoxide capacity per unit of iron. The oxidation-reduction potential of dogs' blood *in vivo* and its variation with  $pO_2$  and  $pCO_2$  were reported by LeMaire (80). Fegler & Banister (81) have surveyed various factors, such as viscosity and temperature, which affect the rate of oxygenation of whole blood.

Studies of the comparative physiology of various hemoglobins continue to point out the property of biological adaptation. Rostorfer & Regdon (82), after overcoming technical difficulties in dealing with the nucleated red cells of ducks, found a marked unexplained difference between the bloods of young and adult animals. In an analysis of the bloods of several elasmobranchs and turtles of various ages, MacCutcheon (83) found no evidence of a fetal type of elasmobranch hemoglobin, but found that fetal turtle hemoglobin persisted for the nearly two years that the animal lives in relatively oxygen-poor mud. The hemoglobins of several round worm parasites, studied by Davenport (84, 85), have remarkably high oxygen affinities and very slow deoxygenation rates and thus may have very slight respiratory properties. Carbon dioxide transport in the snail apparently is carried on without carbonic anhydrase or carbamate linkage, but that in the lobster and crab is more nearly like that in vertebrates, according to Wolvekamp & Kruyt (86). Further data on the differences between fetal and maternal sheep bloods were reported by Barron (87, 88, 89). Jonxis (90) produced evidence that in erythroblastosis fetalis of human infants, adult hemoglobin appears abnormally early and so replaces fetal hemoglobin which is very sensitive to the anti-Rh antibody.

*Gas exchange in tissues: Cerebral.*—Probably the most notable advances in the past three years have been the adaptations of techniques to measure blood flow and oxygen consumption of various organs *in situ*. These avoid the effects of anesthesia and extensive operations, and many of them are applicable to man.

Those studies on the cerebral circulation by Kety, Schmidt and their collaborators and followers have been among the most complete. The nitrous oxide method developed by them has been

improved and subjected to rigid analysis (91). Although perhaps five per cent of extracerebral circulation is included, the effect of this on oxygen consumption should be even smaller, since Loman & Myerson (92) report a high oxygen content of venous blood from the face. The method, originally checked by direct circulatory measurements in monkeys, was further supported by values obtained by Noell & Schneider (93), which were only slightly smaller, although their method entailed considerable operative shock. The use of unilateral jugular blood as representative venous blood was further justified by York *et al.* (94) who found only an exceptional instance of significant difference between the oxygen contents of the two jugulars. A dye dilution method, although not wholly satisfactory, checked the usual values found by the nitrous oxide method [Gibbs *et al.* (95)].

Measurements by Kety, Schmidt and their colleagues (96 to 104) in a variety of experimental and clinical conditions, allow some generalizations. The intrinsic regulation of cerebral flow is such as to maintain nearly constant pH and  $pO_2$  in the venous blood; regulation in regard to changes in  $pCO_2$  (or pH) is more efficient than to oxygen changes; arterial tension and cerebral vascular resistance generally change reciprocally except in coarctation of the aorta, when flow is increased 25 per cent or more; oxygen consumption is maintained nearly constant except in unconsciousness. The importance of carbon dioxide in regulation of cerebral blood flow was confirmed by Gurdjian *et al.* (105) from arterio-venous oxygen measurements alone. Using the nitrous oxide method Abreu *et al.* (106) found very little evidence of cerebral vascular influence from several drugs. Opitz (107) emphasized from general evidence the narrow control of cerebral venous  $pO_2$ . From another aspect, Loeschcke & Loeschcke (108) reported regular uptake of lactate from the arterial blood in the brain, except in severe anoxia when it pours out into the venous blood.

*Gas Exchange in tissues: Myocardial.*—Complicated as it is by multiple asymmetrical venous channels, the circulation of the myocardium has been explored by considering only that portion draining into a single venous channel. Using the coronary sinus in dogs, Eckenhooff and colleagues measured circulation and oxygen first with a bubble flow meter (109, 110), then obtaining samples from a catheter through the jugular vein into the coronary sinus

and using the nitrous oxide method for blood flow (111 to 114). The methods gave similar results.

In man, fear of endocardial damage prevented the use of the method until chance insertion of the venous catheter into the coronary sinus in the course of other studies (Sosman & Dexter (115), Bing *et al.* (116)) proved the procedure safe. Subsequent measurements of myocardial circulation in man, by Bing *et al.* (117, 118), agree with those in dogs. From both, the following generalizations can be made:

- (a) Rather high flow rates (60 to 70 cc. per 100 gm. per min.);
- (b) very high oxygen utilization (8 to 9 cc. per 100 gm. per min.);
- (c) prompt increase in circulation in response to work and oxygen need.

Cytochrome-*c* was found not to increase the already very high oxygen removal from the blood in anoxia according to Hafkenschiel & Eckenhoff (119). Another characteristic measured in dogs is the high lactate and pyruvate utilization accounting for 20 to 70 per cent of the oxygen uptake [Goodale *et al.* (120)]. Aminophyllin, a supposed coronary vasodilant, was found by Faltz *et al.* (121) to reduce the oxygen in coronary venous blood of normal dogs; thus, presumably any coronary dilatation was more than offset by increased cardiac work. Christensen (122) showed that hyperventilation will also produce the electrocardiographic changes considered pathognomonic of myocardial anoxia, and Lange *et al.* (123) demonstrated reversal of anoxic changes with induction of acidosis.

*Gas Exchange in tissues: Splanchnic and renal.*—The techniques of measuring splanchnic circulation and oxygen consumption *in situ* involve catheterization of the hepatic vein and the application of the Fick principle to extraction of bromsulphalein by the liver, both previously described. Oxygen consumption was found to be 20 to 30 per cent of the total oxygen, even in the slower flow of heart failure [Myers & Hickam (124)], or in liver cirrhosis [Bradley, *et al.* (125)]. Intravenous amino acids increased it by up to 50 per cent [Myers & Holland (126)].

The high oxygen consumption of the liver largely removes the argument of Rein (127) who postulated oxygen consumption of the lung linked in some manner to the liver, in order to explain the marked drop in oxygen consumption with hepatectomy.

In contrast to most organs studied, the oxygen consumption of the kidney has been found to depend usually on blood flow. Thus, using renal vein catheterization, Bradley & Halperin (128) found the arteriovenous oxygen difference normally low and unchanged by the reduced renal blood flow of abdominal compression; Cargill & Hickam (129) found it unchanged in most renal disease with reduced blood flow except in some acute processes; Clark & Barker (130) found the oxygen consumption unchanged (6.1 cc. oxygen per 100 gm. per min.) after various diuretics.

*Carbon monoxide.*—Progress continues in elucidating the details of the uptake and elimination of carbon monoxide from the body. Pace *et al.* (131) propose a general formula to predict the degree of saturation at a given time in terms of concentration of carbon monoxide in air, blood volume, and respiratory minute volume, which fits the average of their data but does not explain considerable variation in individual instances. Galdman (132) derived a somewhat different formula which fits the same data. Roughton & Root (133), in studying the elimination of carbon monoxide, found 30 to 40 per cent unaccounted for in blood and expired air in 1 hr., but 96 per cent appeared in 4 hr. Tobias *et al.* (134), by use of radioactive tracer carbon in the carbon monoxide, proved the chief site of this temporary storage to be in the region of the liver, but could find no evidence (less than 0.1 per cent) of conversion to carbon dioxide. Clark *et al.* (135) found an abnormally high disappearance rate of carbon monoxide in turtles and mice and could identify the  $C^{14}$  of administered  $C^{14}O$  in the expired carbon dioxide, in amounts which would correspond in a man to 20 cc. per hr. while breathing 0.07 per cent carbon monoxide. According to Pace *et al.* (136) the elimination rate is lowered with increasing age of subjects.

The physiologic effect of carbon monoxide as a form of anoxia is emphasized by Pitts *et al.* (137) who found the altitude equivalent to be 300 to 400 ft. altitude per one per cent carbon monoxide hemoglobin when measured by the pulse rate after exercise. Using visual intensity discrimination as an index, the altitude equivalent is somewhat greater, according to Halperin *et al.* (138), and somewhat surprisingly, the effect persists for a short time after elimination of the carbon monoxide.

The mechanism of acclimatization to carbon monoxide still eludes explanation. Killick (139) added considerable data by ex-

periments on herself showing a diminution in blood saturation with repeated exposures to the same concentration and believed a change in absorption to occur. Gorbato & Noro (140) found an increased tolerance of rats on repeated exposures, but did not analyze the mechanism.

Speed and success of resuscitation from near-lethal carbon monoxide poisoning in dogs was found by Schwerma *et al.* (141, 142) to be practically the same by several procedures and gas mixtures, although oxygen was found to hasten elimination more than carbon dioxide. Sjöstrand (143), in direct observation on cats, found evidence that cerebral vasodilation was a more prompt and persistent effect of carbon monoxide than changes in cerebrospinal fluid pressure.

The use of carbon monoxide to tag red cells for blood volume measurement has had an upsurge in interest. Root *et al.* (144) in man and Courtice & Gunton in rabbits (145) and man (146) compared it with the dye method and found no clear-cut evidence that body hematocrit varied significantly from that of the venous blood. However, measurements of body hemoglobin solely from alveolar pCO measurements after 15 min. rebreathing, as described by Sjöstrand (147, 148), would appear to be based on tenuous assumptions of alveolar equilibrium and constant blood concentrations.

With respect to the more purely chemical aspects, Fox (149) reported the wide range among hemoglobins of different species of the distribution coefficients (K) between carbon monoxide and oxygen, and the very high K of chlorocruorine from an annelid worm. Melloni & Landon (150) report an effect of high pCO on red cell volume and hemolysis.

*Altitude.*—That the physiologic response to the anoxia of high altitude is represented by a rather wide spectrum of arterial blood findings is apparent from the report of Henson *et al.* (151), as well as that of Miller *et al.* (152) in dogs. The contributions of pulmonary ventilation to this variability and also the benefits of six per cent carbon dioxide in air were presented by Rahn & Otis (153). With the help of their useful graphic presentation of alveolar air they also explained (154) the lower ceiling in respect to pO<sub>2</sub> of rats breathing oxygen compared with air, and the failure of added carbon dioxide to reduce anoxia during oxygen breathing (155). Kline (156), however, did report benefits. The advantage

of moderate hyperventilation was demonstrated strikingly by Houston (157), and Rahn *et al.* (158) showed that moderate hypocapnoea ( $p\text{CO}_2$  greater than 25 mm. Hg) did not affect performance.

The circulatory effects of moderate altitude were studied by Starr & McMichael (159) who found almost complete compensation for a 21 per cent drop in oxygen saturation by an increase in cardiac output (measured by the ballistocardiograph). The ultimate in acute adaptation to altitude (44,800 ft. on oxygen for 15 to 44 min.) was reported by Dill & Penrod (160). The water vapor pressure in the alveolar air, so important at extreme altitudes, was found to be two to three mm. Hg greater than at sea level by Marshall & Specht (161). The mechanisms of high altitude acclimatization have been considerably clarified. Houston & Riley (162) were able to simulate in a high altitude chamber gradual ascent to above 25,000 ft. over the course of 32 days. With the help of numerous measurements on the four human subjects used, they plotted the adaptations as changes in the various gradients in  $p\text{O}_2$  which serve to prevent too great a drop in tissue  $p\text{O}_2$  [Houston (163)]. They point out that hyperventilation, and the secondary reduction in bicarbonate to keep pH constant, constitute the largest factors in adaptation. D'Angelo (164) and Rahn & Otis (165) report similar adaptive changes at lower simulated altitudes. Verzar & Voegtli (166) demonstrated directly the maintenance of a nearly normal  $p\text{O}_2$  in the tissues at moderate altitudes, by analysis of subcutaneous emphysema.

Polycythemia, a small factor in adaptation in the above studies of simulated altitudes, was pointed out in numerous statistics by Hurtado & Aste-Salazar (167) to be prominent in permanent residents at altitude. Pace *et al.* (168) measured the changes in hypoxia tolerance due to artificially induced polycythemia and anemia. The absence of increased myoglobin production during anoxia, however, has been demonstrated by both Poel (169) and Bowen (170). Several aspects of acclimatization by intermittent anoxia were reported by Adams (171) and Altland (172).

Breathing oxygen at elevated pressure to raise the altitude ceiling was intensively studied, the intermittent type by Eckman *et al.* (173) and Fenn *et al.* (174), the constant type by Barach *et al.* (175) and Taylor *et al.* (176). Advantage is reported by all, approaching in some instances quantitative addition of the added

pressure to the  $pO_2$  of the arterial blood. Voluntary increase in pressure during expiration, however [Fenn *et al.* (177)], caused scarcely more benefit than hyperventilation.

Anaerobic metabolism at altitude, as measured by lactic acid accumulation, was usually increased for a given grade of work [Lundin & Ströun (178), Friedeman *et al.* (179), Tepperman & Tepperman (180)]. Furthermore, Asmussen *et al.* (181) found the capacity to develop oxygen debt unchanged at low oxygen pressures. Gemmill (182) reemphasized the increased alveolar-arterial gradient of oxygen during work at altitude. That most mammals have no efficient mechanism of reducing oxygen consumption during anoxia was shown by Rothschiuh (183). A possible exception was found in the young rabbit [Boy & Cheymol (184)]. The interrelationships among oxygen consumption, body temperature, and anoxia were observed by Blood *et al.* (185).

*High oxygen pressures.*—The toxic effects of high concentrations of oxygen on the central nervous system at very high tensions and on the lungs at more moderate tensions have been further studied and the range of effective pressures more carefully delimited. Donald (186) reviewed the extensive British wartime study in relation to submarine work and emphasized the variability and the rather unexpectedly low threshold for toxicity. Grossman & Penrod (187, 188) established that in rats the toxicity for oxygen was closely correlated with the oxygen consumption as modified by low temperatures or thyroid activity. In men at somewhat under one atmosphere  $pO_2$ , Ohlsson (189) has detected toxicity (substernal pain and diminished vital capacity) in a few hours, and intolerable symptoms in 53 to 57 hr. The theory that oxygen toxicity is due to difficult carbon dioxide transport and subsequent tissue anoxia is supported by the observation of Taylor (190) of a progressive fall in  $pO_2$  and rise in  $pCO_2$  in the tissues of cats breathing oxygen. It is difficult to reconcile these reports with that of Farber (191), who subjected men to 5 hr. at two to three atmospheres of  $pO_2$  and to 22 days of one atmosphere without remarkable symptoms, but with some depression of blood formation, which was the main object of his study.

*Asphyxia.*—Under this heading are included reports on various experimental methods of modifying normal breathing as well as those on asphyxia in its usual meaning. Grodius *et al.* (192) and Herber (193) plotted the progressive acid-base changes in induced

asphyxia and emphasized the respiratory acidosis in the stage of collapse. Ivy *et al.* (194), from a demonstration of depressant effect of carbon dioxide during anoxia, Schwerma *et al.* (195) from a study of resuscitation, and Ausherman (196) all strengthen the argument against the therapeutic use of carbon dioxide in asphyxia.

The study of "diffusion respiration" or gas exchange during apnoea in oxygen has physiological interest because (a) the dogs survived well for 30 min. or more, and (b) they tolerated an extreme of carbon dioxide acidosis rarely seen. The bulk of the work is by Draper, Whitehead and colleagues (197 to 201). A similar study by Binet & Strumza (202) is remarkable because of survival in some cases up to 4 hr. Another physiologic trick of probably greater practical usefulness is the "electrophrenic respiration" reported by Sarnoff *et al.* (203, 204, 205) who have demonstrated (a) adequate gas exchange on unilateral phrenic stimulation and (b) complete suppression of spontaneous respiratory movements by this stimulation. Voluntary breath-holding has been again investigated (Stevens *et al.* (206, 207, 208) and Otis *et al.* (209). The work emphasizes the dual control of respiration under the influence of  $p\text{CO}_2$  and  $p\text{O}_2$ , and the greater exchange of oxygen than carbon dioxide because of the properties of the blood and tissues.

*Cardiac output by blood gas measurements.*—Considerable experience has been gained in direct Fick measurements using the venous catheter. The method has been checked against an independent primary method [dye mixing method, Hamilton *et al.* (210)]; it was used as a standard for an improved ballistocardiograph [Nickerson *et al.* (211)]; its limitations and difficulties have been summarized by Warren *et al.* (212); it has served to demonstrate directly the error due to recirculation in the foreign gas method [Werko *et al.* (213)]. A direct photoelectric recording of blood gas concentrations is described by Opitz (214). The use of the method in clinical investigation especially to measure abnormalities of flow in congenital heart disease is reported by Bing and colleagues (215, 216), Dexter *et al.* (217, 218), Maier *et al.* (219), Burchell & Wood (220), and Hamilton *et al.* (221).

Methods of cardiac output measurement based on carbon dioxide equilibrium on rebreathing mixtures of the gas have been reinvestigated by Gray *et al.* (222) and Forsander *et al.* (223), the latter authors attempting to reach equilibrium in the lungs during

quiet breathing. Two recent reports [Roos *et al.* (224), Knutson *et al.* (225)] offer the possibility of measuring mixed venous oxygen by holding the lungs full of six per cent carbon dioxide in helium and observing a plateau of arterial oxygen saturation by an ear oximeter.

*Miscellaneous.*—Systematic studies of changes in blood gases and other effects of various anaesthetic agents have appeared: Nitrous oxide by Barton *et al.* (226), pentothal by Penrod & Hegnauer (227) [also a less extensive report by Greco (228)], barbiturates in general by Swank & Foley (229). A general survey of the effect of anesthetics on carbon dioxide is reported by Krichin & Shkurman (230).

Two new investigations of gaseous nitrogen transport have appeared, one by Stevens *et al.* (231) on elimination by the lung, reinvestigating the relationship to body weight and surface; and the second by Karel & Weston (232) on the femoral arterio-venous difference in dogs, emphasizing that 5 hr. is necessary for full denitrogenation. A mathematical treatment of the subject of inert gas transport was reported by Morales & Smith (233).

Blood gas measurements have been applied to various clinical problems in addition to those already mentioned, with varying degrees of success. The ear oximeter has proven a useful clinical tool in congenital heart disease [Montgomery *et al.* (234), Elam *et al.* (235), Behrmann *et al.* (236)]; as a check on the unreliable clinical sign of cyanosis [Comroe & Botelho (237)] and on cardio-respiratory function [Gullickson *et al.* (238), Kossman & Briller (239), and Ferguson *et al.* (240)]. The arterial saturation in polycythemia vera has been reinvestigated and found normal by Wasserman *et al.* (241) who also discovered technical grounds for the occasional low value found.

Blood gas studies by orthodox methods are reported by Tetel'baum (242) on pulmonary insufficiency, by Kurshakov (243) on circulatory insufficiency, by Makarovskaya (244) on chest wounds, and by Shteinberg (245) on interstitial pneumonia in children. Apperly & Cary (246), from measurements of arterio-venous oxygen differences in the arm in arterial hypertension, believe the arm circulation is a partial "physiological shunt" in this disease.

The attempt of Ray *et al.*, previously reported preliminarily, to develop a test of physiological fitness on the basis of the reduction

time of oxyhemoglobin in the skin capillaries before and after breath-holding, has been shown to correlate with other manifestations of physiological health (247, 248, 249), but the fundamental explanations are not at hand.

Adaptation of the Davies & Brink (283) electrode to tissue  $pO_2$  tensions (in the skin) was reported by Montgomery & Horwitz (250) and offers possibilities as a useful tool. Blood gas changes under three further forms of stress have been investigated: during acceleration, by Gauer *et al.* (251), immersion hypothermia, by Penrod & Rosenhain (252), and in sudden decompression (particularly carbon dioxide) by Paton (253).

*Methodology.*—Photoelectric measurements of oxygen saturation have occupied primary interest recently. Wood and colleagues (254, 255, 256) have modified the Millikan ear oximeter into a more precise instrument and applied the same principle to an oximeter on drawn blood (257, 258). Elam and colleagues (259 to 261), in studies of the ear oximeter, believe the use of histamine for vasodilation of the ear lobe more satisfactory than heat. Paul & Ferguson (262), Hartman *et al.* (263), and Behrmann (264) have modified the oximeter for more satisfactory amplification and recording. A Swedish instrument is also reported [Lindgren (265)]. Apropos of photoelectric measurements of oxygen in drawn blood, there have appeared the reports of Meier *et al.* (266), DeVries & Zylstra (267), and Toffoli (268) and a rather ingenious method for carbon monoxide by Lenggenhager & Lottenbach (269).

Among the chemical methods for blood gases, Whiteley (270) has developed a micro Van Slyke apparatus; Grant (271) has reported the adaptation of the Scholander-Roughton syringe for oxygen capacity measurement; Courtice & Douglas (272) have improved the Haldane blood gas method to agree with the Van Slyke; and Courtice & Simmonds (273) have established the effects of small amounts of carboxyhemoglobin on both methods. Ryan *et al.* (274) report microdiffusion methods for carbon monoxide which agree with standard methods. Scholander *et al.* (275) have added improvements in the measurement of blood carbon dioxide by the Scholander-Roughton syringe. An ingenious ultramicro method for blood gases was described by Scholander & Irving (276). The polarographic method for measuring blood gas tensions has been reexplored by Baumberger *et al.* (277) and found inadequate at present on undiluted blood. Palmer & Morrissey (278)

have described a substitute for the tonometer in equilibrating blood with a gas mixture.

Scholander's ingenious method for analysis of respiratory gases on 0.5 cc. samples (279) and an ultramicro method by the same author and Evans (280) have been published in full. Less fully described methods for carbon dioxide and oxygen were reported by Casella (281) and for carbon monoxide by Soucek (282).

#### LITERATURE CITED

1. RILEY, R. L., LILIENTHAL, J. L., PROEMMEL, D. D., AND FRANKE, R. E., *Am. J. Physiol.*, **147**, 191 (1946)
2. GALDSON, M., AND WOLLACK, A. C., *Am. J. Physiol.*, **151**, 276 (1947)
3. LILIENTHAL, J. L., RILEY, R. L., PROEMMEL, D. D., AND FRANKE, R. E., *Am. J. Physiol.*, **147**, 199 (1946)
4. DIRKEN, M. N. J., AND HEEMSTRA, A. H., *Arch. néerland. physiol.*, **28**, 501 (1947)
5. MALMSTRÖM, G., *Nord. Med.*, **39**, 1327 (1948)
6. DOUGLAS, J. C., RILEY, R. L., AND COURNAND, A., *Federation Proc.*, **8**, 36 (1949)
7. RILEY, R. L., AND COURNAND, A., *Federation Proc.*, **8**, 132 (1949)
8. COURNAND, A., RILEY, R. L., AND HIMMELSTEIN, A., *Federation Proc.*, **8**, 30 (1949)
9. ROOS, A., AND BLACK, H., *Federation Proc.*, **8**, 134 (1949)
10. RAHN, H., MOHNEY, J., OTIS, A. B., AND FENN, W. O., *J. Aviation Med.*, **17**, 173 (1946)
11. RAHN, H., AND OTIS, A. B., *J. Applied Physiol.*, **1**, 717 (1949)
12. OTIS, A. B., RAHN, H., EPSTEIN, M. A., AND FENN, W. O., *Am. J. Physiol.*, **146**, 207 (1946)
13. FENN, W. O., RAHN, H., AND OTIS, A. B., *Am. J. Physiol.*, **146**, 637 (1946)
14. RAHN, H., *Federation Proc.*, **8**, 129 (1949)
15. PENNEYS, R., AND THOMAS, C. B., *Bull. Johns Hopkins Hosp.*, **82**, 470 (1948)
16. CHRISTIENSEN, E. M., URRY, A. G., AND CULLEN, S. C., *Anesthesiology*, **7**, 399 (1946)
17. CONSOLAZIO, W. V., FISHER, M. B., PACE, N., PECORA, L. J., PITTS, G. C., AND BEHNKE, A. R., *Am. J. Physiol.*, **151**, 479 (1947)
18. BARKER, E. S., PONTIUS, R. G., AVIADO, D. M., AND LAMBERTSON, C. J., *Am. J. Med. Sci.*, **217**, 708 (1949)
19. LAMBIE, C. G., AND MORRISSEY, M. J., *J. Physiol. (London)*, **107**, 14 (1947)
20. GALDSTON, M., AND HORWITZ, S. A., *Am. J. Physiol.*, **155**, 420 (1948)
21. HITCHCOCK, F. A., AND STACY, R. W., *Am. J. Physiol.*, **155**, 443 (1948)
22. KYDD, G. H., AND HITCHCOCK, F. A., *Federation Proc.*, **8**, 89 (1949)
23. VAN SLYKE, D. D., HILLER, A., WEISIGER, J. R., AND CRUZ, W. O., *J. Biol. Chem.*, **166**, 121 (1946)
24. FASCIOLLO, J. C., AND CHIODI, H., *Am. J. Physiol.*, **147**, 54 (1946)
25. LAMBERTSON, C. J., CLARK, J. K., AVIADO, D. M., PONTIUS, R. G., BARKER, E. S., AND MOYER, J., *Federation Proc.*, **8**, 90 (1949)

26. COMROE, J. H., JR., AND WALKER, P., *Am. J. Physiol.*, **152**, 365 (1948)
27. WOOD, E. H., *J. Applied Physiol.*, **1**, 567 (1949)
28. PRESTON, S. N., AND ORDWAY, N. K., *Am. J. Physiol.*, **152**, 696 (1948)
29. RILEY, R. L., LILIENTHAL, J. L., PROEMMEL, D. D., AND FRANKE, R. E., *J. Clin. Invest.*, **25**, 139 (1946)
30. DEXTER, L., BURWELL, C. S., HAYNES, F. W., AND SEIBEL, R. E., *J. Clin. Invest.*, **25**, 913 (1946)
31. DOUGLAS, J. C., AND EDHOLM, O. G., *Am. J. Physiol.*, **155**, 434 (1948)
32. WOOD, E. H., TAYLOR, B. E., AND KNUTSON, J., *Federation Proc.*, **8**, 171 (1949)
33. FOWLER, W. S., AND COMROE, J. H., *J. Clin. Invest.*, **27**, 327 (1948)
34. PAULING, L., *Stanford Med. Bull.*, **6**, 215 (1948)
35. WYMAN, J., *Federation Proc.*, **7**, 502 (1948)
36. GRANICK, S., *Blood*, **4**, 404 (1949)
37. BARCROFT, J., *J. Roy. Inst. Pub. Health Hyg.*, **9**, 44 (1946)
38. KING, E. J., GILCHRIST, M., WOOTTON, I. D. P., O'BRIEN, J. R. P., JOPE, H. M., QUELCH, P. E., PETERSON, J. M., STRANGWAYS, D. H., AND RAMSAY, W. N. M., *Lancet*, **254**, 478 (1948)
39. DRABKIN, D. L., *Am. J. Med. Sci.*, **215**, 110 (1948)
40. HOLDEN, H. F., *Australian J. Exptl. Biol. Med. Sci.*, **25**, 57 (1947)
41. MACFARLANE, R. G., KING, E. J., WOOTTON, I. D. P., AND GILCHRIST, M., *Lancet*, **254**, 282 (1948)
42. VARTIAINEN, I., *Ann. Medicinae Internae Fenniae*, **36**, 715 (1947)
43. SHEMIN, D., AND RITTENBERG, D., *J. Biol. Chem.*, **166**, 621 (1946)
44. SHEMIN, D., AND RITTENBERG, D., *J. Biol. Chem.*, **166**, 627 (1946)
45. SHEMIN, D., LONDON, I. M., AND RITTENBERG, D., *J. Biol. Chem.*, **173**, 799 (1948)
46. LONDON, I. M., SHEMIN, D., RITTENBERG, D., *J. Biol. Chem.*, **173**, 797 (1948)
47. ITANO, H. A., AND PAULING, L., *Federation Proc.*, **8**, 209 (1949)
48. GRANT, W. C., AND ROOT, W. S., *Am. J. Physiol.*, **150**, 618 (1947)
49. GRANT, W. C., *Am. J. Physiol.*, **153**, 521 (1948)
50. BERK, L., BURCHENAL, J. H., WOOD, T., AND CASTLE, W. B., *Proc. Soc. Exptl. Biol. Med.*, **69**, 316 (1948)
51. ROSIN, A., AND RACHMILEWITZ, M., *Blood*, **3**, 165 (1948)
52. VERZAR, F., *Schweiz. med. Wochschr.*, **77**, 15 (1947)
53. KLINGELHÖFFER, K. O., *Arch. ges. Physiol. (Pflügers)*, **250**, 31 (1948)
54. POST, R. L., AND SPEALMAN, C. R., *J. Applied Physiol.*, **1**, 227 (1948)
55. HEATH, C. W., *Blood*, **3**, 566 (1948)
56. GIBSON, Q. H., AND HARRISON, D. C., *Lancet*, **253**, 941 (1947)
57. EDER, H. A., FINCH, C., AND MCKEE, R. W., *J. Clin. Invest.*, **28**, 265 (1949)
58. GIBSON, Q. H., *Biochem. J.*, **42**, 13 (1948)
59. GIBSON, Q. H., AND HARRISON, D. C., *Nature*, **162**, 258 (1948)
60. BODANSKY, O., AND HENDLEY, C. D., *J. Clin. Invest.*, **25**, 717 (1946)
61. KIESE, M., *Arch. exptl. Path. Pharmacol.*, **204**, 190 (1947)
62. HUEBNER, W., KIESE, M., STUHLMANN, M., AND SCHWARTZKOPFF, W., *Arch. exptl. Path. Pharmacol.*, **204**, 313 (1947)

63. KIESE, M., AND SCHWARTZKOPFF, W., *Arch. expl. Path. Pharmacol.*, **204**, 267 (1947)
64. KIESE, M., *Arch. expl. Path. Pharmacol.*, **204**, 288 (1947)
65. KIESE, M., *Arch. expl. Path. Pharmacol.*, **204**, 451 (1947)
66. BODANSKY, O., AND GUTMANN, H., *J. Pharmacol. Exptl. Therap.*, **90**, 46 (1947)
67. MOORE, J. C., SHADLE, O. W., AND LAWSON, H. C., *Am. J. Physiol.*, **153**, 322 (1948)
68. RAMSAY, W. N. M., *Biochem. J.*, **40**, 286 (1946)
69. LAWRENCE, W. J., *Med. J. Australia*, **1**, 587 (1947)
70. MAKAROVA, E. I., *Byull. Eksptl. Biol. Med.*, **23**, 300 (1947)
71. ALTSCHULE, M. D., AND LEWIS, H. D., *J. Clin. Invest.*, **27**, 523 (1948)
72. LEWIS, H. D., AND ALTSCHULE, M. D., *Blood*, **4**, 442 (1949)
73. VALLEE, B. L., LEWIS, H. D., ALTSCHULE, M. D., AND GIBSON, J. G., *Blood*, **4**, 467 (1949)
74. KREPS, E. M., *Am. Rev. Soviet Med.*, **4**, 426 (1947)
75. TORDA, C., AND WOLFF, H. G., *Federation Proc.*, **8**, 338 (1949)
76. GORDON, E. E., DARLING, R. C., AND SHEA, E., *J. Applied Physiol.*, **1**, 496 (1949)
77. MORSE, M., CASSELS, D. E., AND HOLDER, M., *Federation Proc.*, **8**, 231 (1949)
78. ENSELME, J., FAVRE-GILLY, J., AND CREYSSSEL, R., *Sang, Le*, **19**, 243 (1948)
79. CHEYMOL, J., AND HENRY, R., *Bull. soc. chim. biol.*, **29**, 81 (1947)
80. LEMAIRE, R., *Compt. rend. soc. biol.*, **141**, 775 (1947)
81. FEGLER, J., AND BANISTER, J., *Quart. J. Exptl. Physiol.*, **33**, 163 (1946)
82. ROSTORFER, H. H., AND REGDON, R. H., *Am. J. Physiol.*, **146**, 222 (1946)
83. MACCUTCHEON, F. H., *J. Cellular Comp. Physiol.*, **29**, 333 (1947)
84. DAVENPORT, H. E., *Proc. Roy. Soc. (London)* [B]**136**, 271 (1949)
85. DAVENPORT, H. E., *Proc. Roy. Soc. (London)* [B]**136**, 255 (1949)
86. WOLVEKAMP, H. P., AND KRUYT, W., *Arch. néerland. physiol.*, **28**, 620 (1947)
87. BARRON, D. H., *Federation Proc.*, **6**, 76 (1947)
88. BARRON, D. H., *Federation Proc.*, **7**, 6 (1948)
89. BARRON, D. H., *Federation Proc.*, **8**, 8 (1949)
90. JONXIS, J. A. P., *Nature*, **161**, 850 (1948)
91. KETY, S. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 476 (1948)
92. LOMAN, J., AND MYERSON, A., *Arch. Neurol. Psychiat.*, **57**, 94 (1947)
93. NOELL, W., AND SCHNEIDER, M., *Arch. ges. Physiol. (Pflügers)*, **250**, 35 (1948)
94. YORK, G. E., HOMBURGER, E., HIMWICH, H. E., *Arch. Neurol. Psychiat.*, **55**, 578 (1946)
95. GIBBS, F. A., MAXWELL, H., AND GIBBS, E. L., *Arch. Neurol. Psychiat.*, **57**, 137 (1947)
96. KETY, S. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 484 (1948)
97. KETY, S. S., HAFKENSCHIEL, J. H., JEFFERS, W. A., LEOPOLD, I. H., AND SHENKIN, H. A., *J. Clin. Invest.*, **27**, 511 (1948)
98. KETY, S. S., SHENKIN, H. A., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 493 (1948)
99. KETY, S. S., POLIS, B. D., NADLER, C. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 500 (1948)

100. SCHMIDT, C. F., AND KETY, S. S., *Trans. Assoc. Am. Physicians*, **60**, 52 (1947)
101. HARMEL, M. H., HAFKENSCHIEL, J. H., AUSTIN, G. M., CRUMPTON, C. W., AND KETY, S. S., *J. Clin. Invest.*, **28**, 415 (1949)
102. HAFKENSCHIEL, J. H., CRUMPTON, C. W., AND MOYER, J. H., *Proc. Soc. Exptl. Biol. Med.*, **71**, 165 (1949)
103. SHENKIN, H. A., KETY, S. S., GRANT, F. C., AND SCHMIDT, C. F., *Am. J. Med. Sci.*, **212**, 755 (1946)
104. HENRY, J. P., GAUER, O., MARTIN, E. E., KETY, S. S., AND KRAMER, K., *Federation Proc.*, **8**, 73 (1949)
105. GURDJIAN, E. S., WEBSTER, J. E., AND STONE, W. E., *Am. J. Physiol.*, **155**, 191 (1949)
106. ABREU, B. E., LIDDLE, G. W., BURKS, A. L., SIMON, A., SUTHERLAND, V., AND GORDAN, G. S., *Federation Proc.*, **7**, 201 (1948)
107. OPITZ, E., *Naturwissenschaften*, **35**, 80 (1948)
108. LOESCHCKE, H. H., AND LOESCHCKE, G., *Arch. ges. Physiol. (Pflügers)*, **249**, 521 (1948)
109. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., AND HARMEL, M., *J. Clin. Invest.*, **26**, 1179 (1947)
110. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., LANDMESSER, C. M., AND HARMEL, M., *Am. J. Physiol.*, **149**, 634 (1947)
111. GOODALE, W. T., LUBIN, M., AND BANFIELD, W. G., *Am. J. Med. Sci.*, **214**, 694 (1947)
112. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., AND LANDMESSER, C. M., *Am. J. Med. Sci.*, **213**, 123 (1947)
113. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., HARMEL, M. H., GOODALE, W. T., LUBIN, M., BING, R. J., AND KETY, S. S., *Am. J. Physiol.*, **152**, 356 (1948)
114. GOODALE, W. T., LUBIN, M., ECKENHOFF, J. E., HAFKENSCHIEL, J. H., AND BANFIELD, W. G., *Am. J. Physiol.*, **152**, 340 (1948)
115. SOSMAN, M. C., AND DEXTER, L., *Radiology*, **48**, 441 (1947)
116. BING, R. J., VANDAM, L. D., GREGOIRE, F., HANDELSMAN, J. C., GOODALE, W. T., AND ECKENHOFF, J. E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 239 (1947)
117. BING, R. J., GOODALE, W. T., ECKENHOFF, J. E., HANDELSMAN, J. C., CAMPBELL, J. A., GRISWOLD, H. E., VANDAM, L. D., HARMEL, M., HAFKENSCHIEL, J. H., LUBIN, M., AND KETY, S. S., *J. Clin. Invest.*, **27**, 525 (1948)
118. BING, R. J., HANDELSMAN, J. C., POWERS, S., AND SPENCER, F., *Federation Proc.*, **8**, 11 (1949)
119. HAFKENSCHIEL, J. H., AND ECKENHOFF, J. E., *Federation Proc.*, **7**, 224 (1948)
120. GOODALE, W. T., HACKEL, D. B., LUBIN, M., AND WILSON, P. P., *Am. J. Physiol.*, **155**, 439 (1948)
121. FALTZ, E. L., RUBIN, A. J., AND STEIGER, W. A., *Federation Proc.*, **8**, 48 (1949)
122. CHRISTENSEN, B. C., *J. Clin. Invest.*, **25**, 880 (1946)
123. LANGE, K., TCHERTKOFF, V., CRAIG, F., AND WEINER, D., *Federation Proc.*, **8**, 312 (1949)
124. MYERS, J. D., AND HICKAM, J. B., *J. Clin. Invest.*, **27**, 620 (1948)
125. BRADLEY, S. E., INGELFINGER, F. J., GROFF, A. E., AND BRADLEY, G. P., *Proc. Soc. Exptl. Biol. Med.*, **67**, 206 (1948)

126. MYERS, J. D., AND HOLLAND, B. C., *J. Clin. Invest.*, **27**, 530 (1948)
127. REIN, H., *Med. Klin. (Munich)*, **42**, 738 (1947)
128. BRADLEY, S. E., AND HALPERIN, M. H., *J. Clin. Invest.*, **27**, 635 (1948)
129. CARGILL, W. H., AND HICKAM, J. B., *J. Clin. Invest.*, **28**, 526 (1949)
130. CLARK, J. K., AND BARKER, H. G., *Federation Proc.*, **8**, 26 (1949)
131. PACE, N., CONSOLAZIO, W. V., WHITE, W. A., BEHNKE, A. R., *Am. J. Physiol.*, **147**, 352 (1946)
132. GALDMAN, D. E., *Federation Proc.*, **6**, 112 (1947)
133. ROUGHTON, F. J. W., AND ROOT, W. S., *Am. J. Physiol.*, **145**, 239 (1946)
134. TOBIAS, C. A., LAWRENCE, J. H., ROUGHTON, F. J. W., ROOT, W. S., AND GREGERSEN, M. I., *Am. J. Physiol.*, **145**, 253 (1946)
135. CLARK, R. T., STANNARD, J. N., AND FENN, W. O., *Science*, **109**, 615 (1949)
136. PACE, N., STRAJMAN, E., AND WALKER, E., *Federation Proc.*, **7**, 89 (1948)
137. PITTS, G. C., AND PACE, N., *Am. J. Physiol.*, **148**, 139 (1947)
138. HALPERIN, M. H., NIVEN, J. I., MCFARLAND, R. A., AND ROUGHTON, F. J. W., *Federation Proc.*, **6**, 120 (1947)
139. KILLICK, E. M., *J. Physiol. (London)*, **107**, 27 (1948)
140. GORBATONE, O., NORO, L., *Acta Physiol. Scand.*, **15**, 77 (1948)
141. SCHWERMA, H., IVY, A. C., AND FRIEDMAN, H., *J. Applied Physiol.*, **1**, 157 (1948)
142. SCHWERMA, H., WOLMAN, W., SIDWELL, A. E., JR., AND IVY, A. C., *J. Applied Physiol.*, **1**, 350 (1948)
143. SJÖSTRAND, T., *Acta Physiol. Scand.*, **15**, 351 (1948)
144. ROOT, W. S., ROUGHTON, F. J. W., AND GREGERSEN, M. I., *Am. J. Physiol.*, **146**, 739 (1946)
145. COURTICE, F. C., AND GUNTON, R. W., *J. Physiol. (London)*, **108**, 405 (1949)
146. COURTICE, F. C., AND GUNTON, R. W., *J. Physiol. (London)*, **108**, 142 (1949)
147. SJÖSTRAND, T., *Acta Physiol. Scand.*, **16**, 201 (1948)
148. SJÖSTRAND, T., *Acta Physiol. Scand.*, **16**, 211 (1948)
149. FOX, H. M., *Nature*, **162**, 20 (1948)
150. MELLONI, G. F., AND LANDON, P., *Policlinico (Rome) Sez. chir.*, **54**, 1364 (1947)
151. HENSON, M., GALDMAN, D. E., CATCHPOLE, H. R., VOLLMER, E. P., KING, B. G., AND WHALEY, R. V., *J. Aviation Med.*, **18**, 149 (1947)
152. MILLER, R. A., HEAGAN, B. S., TAYLOR, C. B., *Am. J. Physiol.*, **150**, 1 (1947)
153. RAHN, H., AND OTIS, A. B., *Am. J. Physiol.*, **150**, 202 (1947)
154. RAHN, H., AND OTIS, A. B., *Proc. Soc. Exptl. Biol. Med.*, **70**, 185 (1949)
155. OTIS, A. B., RAHN, H., AND CHADWICK, L. E., *Proc. Soc. Exptl. Biol. Med.*, **70**, 487 (1949)
156. KLINE, R. F., *Am. J. Physiol.*, **151**, 538 (1947)
157. HOUSTON, C. S., *Am. J. Physiol.*, **146**, 613 (1946)
158. RAHN, H., OTIS, A. B., HODGE, M., EPSTEIN, M. A., HUNTER, S. W., AND FENN, W. O., *J. Aviation Med.*, **17**, 164 (1946)
159. STARR, I., AND MCMICHAEL, M., *J. Applied Physiol.*, **1**, 430 (1948)
160. DILL, D. B., AND PENROD, K. E., *Am. J. Physiol.*, **155**, 433 (1948)
161. MARSHALL, L. H., AND SPECHT, H., *Am. J. Physiol.*, **157**, 299 (1949)
162. HOUSTON, C. S., AND RILEY, R. L., *Am. J. Physiol.*, **149**, 565 (1947)
163. HOUSTON, C. S., *J. Aviation Med.*, **18**, 237 (1947)

164. D'ANGELO, S. A., *Am. J. Physiol.*, **146**, 710 (1946)
165. RAHN, H., AND OTIS, A. B., *Federation Proc.*, **7**, 96 (1948)
166. VERZAR, F., AND VOEGTLI, W., *Helv. Physiol. et Pharmacol. Acta*, **4**, C29 (1946)
167. HURTADO, A., AND ASTE-SALAZAR, H., *J. Applied Physiol.*, **1**, 304 (1948)
168. PACE, N., LOZNER, E. L., CONSOLAZIO, W. V., PITTS, G. C., AND PECORA, L. J., *Am. J. Physiol.*, **148**, 152 (1947)
169. POEL, W. E., *Am. J. Physiol.*, **156**, 44 (1949)
170. BOWEN, W. J., *Federation Proc.*, **8**, 14 (1949)
171. ADAMS, W., *J. Clin. Invest.*, **25**, 912 (1946)
172. ALTLAND, P. D., *Federation Proc.*, **8**, 3 (1949)
173. ECKMAN, M., BARACH, B., FOX, C., RUMSEY, C. C., SOMKIN, E., AND BARACH, A. L., *J. Aviation Med.*, **18**, 565 (1947)
174. FENN, W. O., RAHN, H., OTIS, A. B., AND CHADWICK, L. E., *J. Applied Physiol.*, **1**, 773 (1949)
175. BARACH, A. L., ECKMAN, M., ECKMAN, I., GINSBURG, E., RUMSEY, C. C., *J. Aviation Med.*, **18**, 139 (1947)
176. TAYLOR, C. B., MARBARGER, J. P., AND POWER, M. H., *J. Applied Physiol.*, **1**, 45 (1948)
177. FENN, W. O., RAHN, H., OTIS, A. B., AND CHADWICK, L. E., *J. Applied Physiol.*, **1**, 752 (1949)
178. LUNDIN, G., AND STRÖUN, G., *Acta Physiol. Scand.*, **13**, 253 (1947)
179. FRIEDEMANN, T. E., IVY, A. C., HARRIS, S. C., SHEFT, B. B., AND KINNEY, V. M., *Quart. Bull. Northwestern Univ. Med. School*, **21**, 228 (1947)
180. TEPPERMAN, J., AND TEPPERMAN, H. M., *J. Clin. Invest.*, **27**, 176 (1948)
181. ASMUSSEN, E., DOBELN, M. V., AND NIELSEN, M., *Acta Physiol. Scand.*, **15**, 57 (1948)
182. GEMMILL, C. L., *J. Aviation Med.*, **18**, 483 (1947)
183. ROTHSCHUH, K. E., *Arch. ges. Physiol. (Pflügers)*, **249**, 175 (1947)
184. BOY, G., AND CHEYMOL, J., *Bull. soc. chim. biol.*, **28**, 382 (1946)
185. BLOOD, F. R., GLOVER, R. M., HENDERSON, J. B., AND D'AMOUR, F. E., *Am. J. Physiol.*, **156**, 62 (1949)
186. DONALD, K. W., *Brit. Med. J.*, **I**, 667 (1947)
187. GROSSMAN, M. S., AND PENROD, K. E., *Am. J. Physiol.*, **156**, 177 (1949)
188. GROSSMAN, M. S., AND PENROD, K. E., *Am. J. Physiol.*, **156**, 182 (1949)
189. OHLSSON, W. T. L., *Acta Med. Scand.*, **128**, 4 (1947)
190. TAYLOR, H. J., *J. Physiol. (London)*, **108**, 264 (1949)
191. FARBER, V. B., *Klin. Med. (U.S.S.R.)*, **26**, 46 (1948)
192. GRODIUS, F. S., LEIN, A., AND ADLER, H. F., *Am. J. Physiol.*, **147**, 433 (1946)
193. HERBER, F. J., *Am. J. Physiol.*, **152**, 687 (1948)
194. IVY, J. H., GRODIUS, F. S., ADLER, H. F., AND SNAPP, F. E., *J. Aviation Med.*, **18**, 577 (1947)
195. SCHWERMA, H., IVY, A. C., BURKHARDT, W. L., AND THOMETZ, A. F., *Am. J. Physiol.*, **156**, 145 (1949)
196. AUSHERMAN, H. M., *Anesthesia & Analgesia*, **27**, 172 (1948)
197. ROTH, L. W., WHITEHEAD, R. W., DRAPER, W. B., *Anesthesiology*, **8**, 294 (1947)

198. DRAPER, W. B., WHITEHEAD, R. W., AND SPENCER, J. N., *Anesthesiology*, **8**, 524 (1947)
199. WHITEHEAD, R. W., SPENCER, J. N., PARRY, T. M., AND DRAPER, W. B., *Anesthesiology*, **10**, 54 (1949)
200. SPENCER, J. N., DRAPER, W. B., PARRY, T. M., WHITEHEAD, R. W., *Federation Proc.*, **7**, 119 (1948)
201. PARRY, T. M., SPENCER, J. N., DRAPER, W. B., WHITEHEAD, R. W., ARENDS, R. L., *Federation Proc.*, **8**, 323 (1949)
202. BINET, L., AND STRUMZA, M. V., *Compt. rend.*, **225**, 12 (1947)
203. SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L., *Am. J. Physiol.*, **155**, 1 (1948)
204. WHITTENBERGER, J. L., SARNOFF, S. J., AND HARDENBERGH, E., *J. Clin. Invest.*, **28**, 124 (1949)
205. SARNOFF, S. J., WHITTENBERGER, J. L., HARDENBERGH, E., *Am. J. Physiol.*, **155**, 203 (1948)
206. STEVENS, C. D., FERRIS, E. B., WEBB, J. P., ENGEL, G. L., AND LOGAN, M., *J. Clin. Invest.*, **25**, 723 (1946)
207. ENGEL, G. L., FERRIS, E. B., WEBB, J. P., AND STEVENS, C. D., *J. Clin. Invest.*, **25**, 729 (1946)
208. FERRIS, E. B., ENGEL, G. L., STEVENS, C. D., AND WEBB, J. P., *J. Clin. Invest.*, **25**, 734 (1946)
209. OTIS, A. B., RAHN, H., AND FENN, W. O., *Am. J. Physiol.*, **152**, 674 (1948)
210. HAMILTON, W. F., RILEY, R. L., ATTYUH, A. M., COURNAND, A., FOWELL, D. M., HIMMELSTEIN, A., NOBLE, R. P., REMINGTON, J. W., RICHARDS, D. W., WHEELER, N. C., AND WITHAM, A. C., *Am. J. Physiol.*, **153**, 309 (1948)
211. NICKERSON, J. L., WARREN, J. V., BRANNON, E. S., *J. Clin. Invest.*, **26**, 1 (1947)
212. WARREN, J. V., STEAD, E. A., AND BRANNON, E. S., *Am. J. Physiol.*, **145**, 458 (1946)
213. WERKO, L., BERSEUS, S., AND LAGERLOF, H., *J. Clin. Invest.*, **28**, 516 (1949)
214. OPITZ, E., *Arch. ges. Physiol. (Pflügers)*, **250**, 56 (1948)
215. BING, R. J., VANDAM, L. D., AND GRAY, F. D., *Bull. Johns Hopkins Hosp.*, **80**, 107, 121, 323 (1947)
216. HANDELSMAN, J. C., BING, R. J., CAMPBELL, J. A., AND GRISWOLD, H. E., *Bull. Johns Hopkins Hosp.*, **82**, 615 (1948)
217. DEXTER, L., HAYNES, F. W., BURWELL, C. S., EPPINGER, E. C., SEIBEL, R. E., AND EVANS, J. M., *J. Clin. Invest.*, **26**, 547 (1947)
218. DEXTER, L., HAYNES, F. W., BURWELL, C. S., EPPINGER, E. C., SAGERSON, R. P., AND EVANS, J. M., *J. Clin. Invest.*, **26**, 554, 561 (1947)
219. MAIER, C., VOLKMANN, M., WIESINGER, K., BUBB, W., FISCHER, F., AND MÜLLY, K., *Cardiologia*, **14**, 257 (1949)
220. BURCHELL, H. B., AND WOOD, E. H., *J. Applied Physiol.*, **1**, 560 (1949)
221. HAMILTON, W. F., WINSLOW, J. A., AND HAMILTON, W. F., JR., *Federation Proc.*, **8**, 66 (1949)
222. GRAY, F. D., BING, J. R., AND VANDAM, L., *Am. J. Physiol.*, **151**, 245 (1947)
223. FORSANDER, C. A., KRAMER, H., MARTIN, C. J., WHITE, C., AND BAZETT, H. C., *Federation Proc.*, **8**, 49 (1949)

224. ROOS, A., ELAM, J. O., NEVILLE, J. F., JR., AND WHITE, H. L., *Federation Proc.*, **7**, 104 (1948)
225. KNUTSON, J., TAYLOR, B. E., AND WOOD, E. H., *Federation Proc.*, **8**, 87 (1949)
226. BARTON, G. D., WICKS, W. R., AND LIVINGSTONE, H. M., *Anesthesiology*, **7**, 505 (1946)
227. PENROD, K. E., AND HEGNAUER, A. H., *Am. J. Physiol.*, **153**, 81 (1948)
228. GRECO, G., *Boll. soc. ital. biol. sper.*, **24**, 8 (1948)
229. SWANK, R. L., AND FOLEY, J. M., *J. Pharmacol. Exptl. Therap.*, **92**, 381 (1948)
230. KRICHIN, D. G., AND SHKURMAN, P. O., *Vrachebnoe Delo*, **27**, 23 (1947)
231. STEVENS, C. D., RYDER, H. W., FERRIS, E. B., AND INATOME M., *J. Aviation Med.*, **18**, 111 (1947)
232. KAREL, L., AND WESTON, R. E., *Am. J. Physiol.*, **151**, 71 (1947)
233. MORALES, M. F., AND SMITH, R. E., *Bull. Math. Biophys.*, **10**, 191 (1948)
234. MONTGOMERY, G. E., JR., GERACI, J. E., PARKER, R. L., AND WOOD, E. H., *Proc. Staff Meetings Mayo Clinic*, **23**, 169 (1948)
235. ELAM, J. O., ROOS, A., AND NEVILLE, J. F., *Am. J. Physiol.*, **155**, 435 (1948)
236. BEHRMANN, V. G., HARTMAN, F. W., ZIEGLER, R. F., AND LAM, C. R., *Federation Proc.*, **8**, 9 (1949)
237. COMROE, J. H., JR., AND BOTELHO, S. Y., *Am. J. Med. Sci.*, **214**, 1 (1947)
238. GULLICKSON, G., ELAM, J. O., HAMMOND, H., PAINE, J. R., AND VARCO, R. L., *Am. Heart J.*, **35**, 940 (1948)
239. KOSSMAN, C. E., AND BRILLER, S. A., *Proc. Soc. Exptl. Biol. Med.*, **65**, 63 (1947)
240. FERGUSON, J. K. W., FINLAYSON, D. M., AND HILLIARD, I. M., *Federation Proc.*, **8**, 44 (1949)
241. WASSERMAN, L. R., DOBSON, R. L., LAWRENCE, J. H., *J. Clin. Invest.*, **28**, 60 (1949)
242. TETEL'BAUM, A. G., *Klin. Med. U.S.S.R.*, **25**(1), 45 (1947)
243. KURSHAKOV, N. A., AND SHARAFYAN, M. A., *Klin. Med. U.S.S.R.*, **25**(8), 36 (1947)
244. MAKAROVSKAYA, TS. D., *Klin. Med. U.S.S.R.*, **25**(4), 58 (1947)
245. SHTEINBERG, D. E., *Voprosy Pediat. i Okhrany Materinstva i Detstva*, **15**(4), 53 (1947)
246. APPERLY, F. L., CARY, M. K., *Am. J. Med. Sci.*, **211**, 467 (1946)
247. RAY, G. B., *Am. J. Physiol.*, **147**, 622 (1946)
248. RAY, G. B., RAY, L. H., AND JOHNSON, J. R., *Am. J. Physiol.*, **147**, 630 (1946)
249. RAY, G. B., JOHNSON, J. R., AND RAY, L. H., *Am. J. Physiol.*, **147**, 636 (1946)
250. MONTGOMERY, H., AND HORWITZ, O., *J. Clin. Invest.*, **27**, 550 (1948)
251. GAUER, O., HENRY, J. P., MARTIN, E. E., MAHER, P. J., *Federation Proc.*, **8**, 54 (1949)
252. PENROD, K. E., AND ROSENHAIN, F. R., *Federation Proc.*, **8**, 126 (1949)
253. PATON, W. D. M., *J. Physiol. (London)*, **107**, 1P (1948)
254. GERACI, J. E., MONTGOMERY, G. E., AND WOOD, E. H., *Federation Proc.*, **7**, 41 (1948)
255. KNUTSON, J. R. B., AND WOOD, E. H., *Am. J. Physiol.*, **155**, 448 (1948)
256. WOOD, E. H., GERACI, J. E., AND GROOM, D. L., *Federation Proc.*, **7**, 137 (1948)

257. MONTGOMERY, G. E., GERACI, J. E., AND WOOD, E. H., *Federation Proc.*, **7**, 81 (1948)
258. GROOM, D. L., WOOD, E. H., BURCHELL, H. B., AND PARKER, R. L., *Proc. Staff Meetings Mayo Clinic*, **23**, 601 (1948)
259. ELAM, J. O., EHRENHAFT, J. L., ELAM, W. N., AND WHITE, H. L., *Federation Proc.*, **8**, 40 (1949)
260. NEVILLE, J. F., JR., ELAM, J. O., SUGIOKA, K., AND ROOS, A., *Federation Proc.*, **8**, 118 (1949)
261. SLEATOR, W., ELAM, J. O., KILIAN, D. J., ELAM, W. N., *Federation Proc.*, **8**, 147 (1949)
262. PAUL, W., AND FERGUSON, J. K. V., *Rev. can. biol.*, **7**, 193 (1948)
263. HARTMAN, F. W., BEHRMANN, V. G., AND CHAPMAN, F. W., *Am. J. Clin. Path.*, **18**, 1 (1947)
264. BEHRMANN, V. G., *Federation Proc.*, **7**, 7 (1948)
265. LINDGREN, I., *Stenska Läkartidn.*, **44**, 401 (1947)
266. MEIER, R., PELLMONT, B., AND WIRZ, E., *Helv. Physiol. et Pharmacol. Acta*, **5**, C43 (1947)
267. DEVRIES, K. J., ZYLSTRA, W. G., *Nederland. Tijdschr. Geneesk.*, **92**, 3952 (1948)
268. TOFFOLI, C., *Ann. chim. applicata*, **38**, 444 (1948)
269. LENGGENHAGER, K., AND LOTTENBACH, K., *Schweiz. med. Wochschr.*, **78**, 370 (1948)
270. WHITELEY, A. H., *J. Biol. Chem.*, **174**, 947 (1948)
271. GRANT, W. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 60 (1947)
272. COURTICE, F. C., AND DOUGLAS, C. G., *J. Physiol. (London)*, **105**, 345 (1947)
273. COURTICE, F. C., AND SIMMONDS, W. J., *J. Physiol. (London)*, **107**, 300 (1948)
274. RYAN, M. T., NOLAN, J., AND CONWAY, E. J., *Biochem. J.*, **42**, 64 (1948)
275. SCHOLANDER, P. F., FLEMISTER, S. C., AND IRVING, L., *J. Biol. Chem.*, **160**, 173 (1947)
276. SCHOLANDER, P. F., AND IRVING, L., *J. Biol. Chem.*, **169**, 561 (1947)
277. BAUMBERGER, P., MARKUS, G., AND BARDWELL, K., *Federation Proc.*, **8**, 8 (1949)
278. PALMER, A. J., AND MORRISSEY, M. J., *Med. J. Australia*, **1** (1), 401 (1948)
279. SCHOLANDER, P. F., *J. Biol. Chem.*, **167**, 235 (1947)
280. SCHOLANDER, P. F., AND EVANS, H. J., *J. Biol. Chem.*, **169**, 551 (1947)
281. CASELLA, C., *Boll. soc. ital. biol. sper.*, **23**, 32, 35 (1947)
282. SOUCEK, B., *Schweiz. med. Wochschr.*, **78**, 743 (1948)
283. DAVIES, P. W., AND BRINK, F., *Rev. Sci. Instruments*, **13**, 524 (1942)

## ENERGY METABOLISM<sup>1</sup>

BY WILLIAM H. CHAMBERS AND WILLIAM H. SUMMERSON

*Medical Division, Army Chemical Center, Maryland*

The ever broadening ramifications of research in energy metabolism into the various specialized fields of both theoretical and applied physiology are well illustrated by viewing the publications of the past two years in the light of the chapters on energy metabolism in preceding issues of *Annual Review of Physiology*. Correlated studies of respiratory metabolism and direct heat production by calorimetry are gradually being superseded by broader and more detailed research on temperature regulation and heat exchange. For example, in Volume I Murlin discusses Poulton's critique of direct and indirect heat calculations and Benedict's valedictory monograph on "Vital Energetics." In Volume III Carpenter notes that "relatively few articles on direct calorimetry have appeared." The number has dwindled appreciably since then. Publications from only one laboratory have been found in the present period (1, 2). However, studies on heat loss have become an important factor in applied physiology. In agriculture a new series of publications has appeared on "Environmental Physiology," the first of which describes the establishment of an Animal Psychroenergetic Laboratory at the University of Missouri. The scope of research in this field is reviewed (3).

With the decline in direct heat measurements, oxygen consumption has become the common measure of energy production in the whole organism, despite the well-known variation in the caloric value of oxygen with the type of fuel being metabolized. For the intact animal, the continuous production of energy, even from the various known energy-yielding processes which do not require immediate association with oxidative reactions, must be ultimately related to oxygen consumption. In the case of isolated tissues or organs, however, where research on an increasing scale is contributing much valuable knowledge concerning the many basic mechanisms involved in the physiology of the whole organism, the relation between oxygen consumption and energy production is not necessarily a simple or even a direct one, and certain aspects of this problem logically take their place in this review.

<sup>1</sup> This review covers the period from July 1947 through June, 1949.

## METABOLISM OF THE ANIMAL AS A WHOLE

*Basal metabolism standards.*—In a comprehensive review of the relation of body size to metabolic rate, Kleiber (4) has assembled and analyzed the comparable data which have appeared since his 1932 publication. Plotting calories per day against body weight, both on a logarithmic scale, for data on 12 homeothermic mammalian species ranging from mouse (0.021 kg.) to cow (600 kg.), the regression line is found to have a slope of 0.756. Considering a coefficient of variation in metabolic rate per unit size of 7 per cent, this is not significantly different from his 1932 value (slope 0.739) or from Brody's figure of 0.734. Kleiber recommends the use of body weight  $^{0.75}$  (kg. $^{3/4}$ ) for the representative unit of "metabolic body size." whereas Brody (5, p. 373) suggested kg. $^{0.7}$ , the "physiologically effective body size," as the reference base for basal metabolism of mature animals of different species. The former author (4) notes that the establishment of a significant difference between regression slopes of kg. $^{3/4}$  and kg. $^{2/3}$  (approximate surface area) would require a series of mature animals covering a ninefold range in weight. Hence, the reference unit is used mainly in the comparison of animal species. Within the few species which have a sufficient difference in weight of mature individuals to plot a regression line, the coefficients are given as kg. $^{0.76}$  for mice, kg. $^{0.67}$  for rats, and kg. $^{0.82}$  for rabbits. For dogs, differences in technique should be noted in comparing the coefficient of kg. $^{0.63}$  [Lusk (103), Kunde (104)] with Galvão's recent figure of kg. $^{0.90}$  (6).

The well-known precise conditions required and attained in determining basal metabolism in human subjects are difficult to achieve in other species. Also, comparable anatomic surface area equations for many of the other species are not available. For practical purposes of interspecific comparisons among animals, the most convenient and accurate measurement of body size is body weight, and a power function of weight is the most useful and accurate standard. "The age-weight-height interrelation for man is of quite a different order than for farm animals" [Brody (5)], hence this standard appears most useful for intraspecific comparisons where strictly basal conditions can be realized.

Two authors discuss the broader aspects of physiological standards on the basis of quantitative relations. Adolph (7) presents a nomogram for a wide range of mammalian species relating

34 biological characteristics to some power of body weight and points out the numerous correlations which may be derived therefrom. This concept should stimulate research in comparative physiology although scarcity of accurate data limits the present application of the nomogram. Keys' paper (8) concerns standards of normality, particularly in man. By way of illustration, data are given on evaluating the individual in relation to basal metabolism, blood cholesterol, fatness, age, and eye color. Emphasis is placed on the need for more consideration of individual variation.

*Basal metabolism.*—Comparatively few reports on basal metabolism *per se* have appeared recently. In the careful study of girls and young women in the subtropical climate of southern Arizona by Thompson, Cox & Ridgway (9), 887 respirometer tests were conducted on 218 subjects in the age range from 18 to 24 years under basal conditions. Tests on each subject were continued daily until two tests on different days agreed within 5 per cent. The data are analyzed on the basis of the 5 per cent check tests and those outside the 5 per cent agreement. The usual fall in metabolism in kilocalories per square meter (kcal. per sq. m.) was found between the ages of 14 and 19 years, but the level was lower than that reported by most other investigators. Mean values of 31.1 and 31.5 kcal. per sq. m. per hr. for women 18 to 23 years old are in the range of the earlier work of Hardy, Milhorat & DuBois (10). By a comparison of basal metabolism of girls 18 years old with the mean annual temperature in midwestern states, adaptation to environmental temperature is illustrated by values ranging from 35.7 kcal. per sq. m. per hr. in Minnesota (41.6°) to 31.2 kcal. in southern Arizona (67.2°).

Another series of experiments on the effect of tropical climate on basal metabolism are reported by Galvão (11, 12). Regression lines from data on lean and well proportioned men in Brazil are compared with those from the northern United States. Power functions of weight from equations for lean Brazilians and well proportioned Brazilians are respectively  $W^{0.83}$  and  $W^{0.78}$  and for lean Americans and well proportioned Americans are  $W^{0.69}$  and  $W^{0.67}$ . Although the difference between  $W^{0.83}$  and  $W^{0.78}$  is not significant, the heat production of lean men in the tropics was about 7 per cent below that of the same weight range group of lean Americans. It is concluded that the surface law applies in cold but not in

warm climates. The statement that "in warmer climates . . . heat production . . . is independent of heat loss through the body surface" is somewhat surprising and emphasizes the need for further research on this problem, using respiratory metabolism with partitioned direct heat determinations under strictly imposed basal conditions at thermal neutrality. In clinical basal metabolism tests on 250 Brazilian girls aged 8 to 18 years, 193 fell within  $\pm 10$  per cent of the Boothby-Sandiford standards [Orsini (13)].

A low basal metabolism accompanying loss of body weight was observed in 84 representative German men, the results being in accordance with Benedict's early studies on undernutrition [Kaller & Reller (14)]. Some of the 34 women subjects also studied showed a low metabolism inconsistent with the slight or negative weight losses. The general lack of undernutrition, despite the low official ration, is attributed by the authors to the availability of supplemental food.

Fundamental information on basal metabolism of animals is coming from studies of related problems. For sheep fed at five levels from one-half to twice maintenance, Marston (15) finds a mean basal metabolism of 68 kcal. per  $W^{0.73}$  per 24 hr. On extrapolation of the regression line for maintenance and above back to zero, the "true basal" would be 54.6 kcal. per  $W^{0.73}$  per day compared to 51.9 kcal. per  $W^{0.73}$  per day for steers (Forbes' data). The author does not comment on the fact that the determinations at one-half maintenance level fall above the extrapolated regression line.

Metabolism and cardiorespiratory activity in cattle and mules have been related by Brody and colleagues. Among many points of interest are that "resting metabolism" and surface area in growing beef cattle increase with  $W^{0.6}$  whereas ventilation rate increases with  $W^{1.0}$  (16). Similar determinations on four growing mules showed that "resting metabolism" increases with  $W^{0.64}$  and ventilation rate with  $W^{0.73}$  (17).

Morrison recorded the oxygen consumption of small mammals under basal conditions and during activity (18, 19). Expressed as cal. per gm.  $^{0.73}$  per hr., basal metabolism varied from 4.5 cal. for bats to 49 cal. for longtail shrews with a 17.1 cal. average for rodents. Daily activity cycles increased the metabolism of the wild pine mouse only 4 per cent, whereas the increment in flying squirrels was 85 per cent and was much higher than 85 per cent in bats.

*Exercise.*—Ketones may be retained in the muscle to the extent of about six times the amount oxidized if the level in the blood is high during and after exercise according to the calculations of Heilesen (20). If the blood ketones are low, the amounts retained and oxidized are about equal. The calculations of ketone and fat oxidation in men exercising in the postabsorptive state after a ketogenic diet were made from data on respiratory metabolism, blood ketones, and blood minute volume.

The basal metabolism and energy expenditure for various activities of groups of boys and girls within the age range of 7 to 14 years have been measured by Taylor and co-workers (21, 22, 23). The increase over basal level varied from about 50 per cent when listening to the radio to over 200 per cent when cycling.

Age and training are factors in the speed of the rapid recovery phase of oxygen debt after mild exercise for three minutes at an oxygen consumption of about 1,000 cc. per min. above the resting level. The time required to reach one-half recovery on oxygen and carbon dioxide is the constant measured by Berg (24, 25). Raising the alkali reserve hastened carbon dioxide recovery by 23 per cent and oxygen recovery by 13 per cent in one experienced subject.

*Specific dynamic action (S.D.A.).*—The comprehensive and critical review by Sadhu (26) of the early and recent theories on S.D.A. should stimulate renewed research interest in this phase of intermediary metabolism. Experimental data to test some of the newer theories are also presented. The effect of pyruvic acid, lactic acid, thiouracil feeding, pyridoxine feeding and deficiency, vitamins E and A and thiamine on the S.D.A. of glycine, glutamic acid, cystine, phenylalanine, tyrosine, and glucose was determined in the rat. Transamination counterbalancing deamination in the metabolism of amino acids is proposed as a new explanation for the differences in S.D.A. found in the individual amino acids. Details are published in several other articles (27, 28, 29). Barker's critique (30, p. 58) notes the inconsistencies with older experiments on other animal species.

The effect on S.D.A. and nitrogen balance of a mild deficiency in one essential amino acid has been used by Anderson & Nasset (31) to determine efficiency of food utilization. Reduction of DL-isoleucine to one-third the quantity in the "complete" amino acid mixture diet of the rat caused an increase in S.D.A. and in nitrogen maintenance requirement. There was no significant effect

on extra heat production from reducing the DL-methionine or DL-valine content or from substituting relatively large amounts of glycine for glutamic acid in the diet; however, DL-methionine deficiency caused a rise in nitrogen maintenance requirement. No theory is offered to explain why lowering its isoleucine content should increase the S.D.A. of the diet by approximately 100 per cent.

Data from human subjects on the S.D.A. of high protein and high carbohydrate meals containing about 1,000 kcal. have been presented by Glickman, Mitchell, Lambert & Keeton (32). Their analysis shows an acceleration phase of extra heat production for 1.5 to 2.5 hr. post prandium and then a deceleration which follows the law of diminishing returns. From the derived equations the total S.D.A. as calculated from 6.5 hr. determinations is estimated to be 169 kcal. for a total of 16 hr. after the high protein meal and 103 kcal. for 12 hr. after the high carbohydrate meal or 17.0 per cent and 9.6 per cent respectively of the ingested calories. These figures are higher than those in the earlier literature on account of the longer time period.

*Diet and undernutrition.*—A series of studies on the effect of the fat level of the diet on general nutrition in the rat are reported by Deuel, Scheer, and co-workers. Growth, recovery from undernutrition, lactation, efficient utilization of food and storage of fat are some of the metabolic functions which reach their optimum when the fat content of the diet is between 20 and 40 per cent (33 to 36). Black, French & Swift compared diets containing 2 or 30 per cent fat (37, 38, 39). Measurements of respiratory metabolism showed that rats on a high fat diet had a lower heat production and stored more fat in the body than the low fat group. Observations of fluctuations in activity during 48 hr. and during super-maintenance feeding confirmed the relative advantage of the 30 per cent fat diet.

The metabolic abnormalities in starvation diabetes have been reviewed by Lundbaek (40). Rats on a high fat diet live longer, are less easily exhausted, and exhibit a lower voluntary activity during a subsequent fast than those on high carbohydrate or protein [Samuels, Gilmore & Reinecke (41)].

Beattie & Herbert (42, 43) took advantage of the unusual opportunity to study the respiratory metabolism of German civil prisoners who had subsisted on a 1,750 kcal. ration from 1945 to

1946. An interesting discussion of the relation of metabolic rate to weight and surface area during starvation and recovery is included.

Convalescent or growing individuals can use up to 4 gm. per kg. per day of dietary protein for storage as new tissue, provided nonprotein energy is supplied at approximately 1,500 kcal. per sq. m. per day according to the experiments of Benditt and co-workers (44, 45). Another aspect, caloric restriction, of this general problem has been presented by Bosshardt, Paul, O'Doherty & Barnes (46). Reference is also made to the recent review on proteins by Deuel (47).

*Hormones.*—Barker's 1949 review (30) of metabolic functions of the endocrine system includes the effect of various hormones on energy exchange. An anterior pituitary substance which increases oxygen consumption and cardiac output other than through thyroid mediation is postulated by White, Heinbecker & Rolf (48) on the basis of administering anterior lobe extract to thyroidectomized dogs. The thyrotrophic action was demonstrated in normal and hypophysectomized animals.

Thiouracil (0.1 and 0.2 per cent in the diet) depressed the total metabolism of growing rats during a feeding period of 70 days. Body analyses at the end of the experiment showed significant body storage of energy mainly as fat which corresponded to the decrease in heat production [Bratzler, Barnes & Swift (49)]. When hyperthyroidism was produced in rats by including 45 mg. per day of iodinated casein in the diet, Mukherjee & Mitchell (50) noted that the ratio of minimum endogenous nitrogen metabolism to basal metabolism was not significantly altered from the value of 1.53 for the controls, although basal metabolism was elevated approximately 85 per cent. In a study of biological values of protein in human subjects between the ages of 21 and 31 years, Hawley, Murlin, Nasset & Szymanski (51) found a ratio of endogenous urinary nitrogen to basal metabolism of 1.19 in 6 women and 1.32 in 7 men. The low average basal metabolism of 32.5 kcal. per sq. m. per hr. in the women and 35.9 in the men is of interest in connection with climatic effects noted above.

Evidence that the adrenal cortex is involved in the calorogenic action of thyroxine has been presented by Hoffmann, Hoffmann & Talesnik (52). Adrenalectomy reduced the rise in oxygen consumption produced by thyroxine, but this response was restored to normal by cortical extract. The increase in oxygen consumption

accompanied by an elevation of rectal temperature during and after the intravenous infusion of adrenalin in the anesthetized cat is reduced to about one-third, with some fall in body temperature, if the skin has been removed. Whitcher & Griffith (53) suggest that the normal adrenalin reaction is mediated through vasoconstriction and consequent increase in body temperature.

The role of the gonads is illustrated by the following references. The fall in heat production of normal women in the warm zone (26° to 32°C.) did not occur in postmenopausal subjects [Hardy, Shorr, & DuBois (54)], but the normal metabolic reaction was restored by the administration of estrogens. The metabolism of growing male rats has been determined by Quimby, Phillips & White (55) during chronic inanition and recovery. The reduction in total respiratory metabolism from the high recovery phase level when testosterone was administered is attributed to pituitary inhibition (56).

*Surface area and basal metabolism.*—Interest continues in the century-old problem of the causal relationship between surface area and basal metabolism. Kleiber (4) discusses five theories and considers two of them basically sound, namely, relation to heat transfer and relation to blood circulation. True basal metabolism determinations demand a condition of thermal neutrality, heat loss equivalent to heat production. A simple gradient calorimeter has been devised by Prouty, Barrett & Hardy (2) with a precision of  $\pm 2$  per cent for individual periods under favorable conditions. The cat experiment cited shows 2.22 kcal. per 30 min. for direct heat and 2.20 kcal. for oxygen consumption, although the cat is a poor subject for thermal stress in comparison with man (1).

Several recent reviews have demonstrated the extent to which the war-stimulated research in environmental physiology has broadened our knowledge of the complexity of the temperature regulating mechanisms involved in responses to heat stress. Some of the difficulties encountered in applying equations from physical laws to heat loss from the body surface are noted by Machle & Hatch (57). Heat loss by radiation can be related to surface area by the Stefan-Boltzman equation; however, recent experimental determinations of the ratio of effective radiation area to total body surface area in man have varied from 0.71 to 0.93 (57). The mean radiation temperature of the body surface is a composite of various skin areas, each with a different temperature, which in the pioneer work of Hardy & DuBois (58) ranged from 30.6° to 35.0°C. under

basal conditions, and may vary from subject to subject [Hertzman & Randall (59)]. Heat loss by convection involves body surface area and skin temperatures, but these factors have received little attention compared to the major one of air flow. The relation between effective radiation area and convection area has not been established. The numerous recent studies on heat loss by evaporation at environmental temperatures above the zone of thermal neutrality emphasize the difficulty of deriving a mathematical expression for this function. Skin temperature is an important factor in relating effective evaporative surface to total surface area (57). The difficulties involved in accurately measuring heat loss, exclusive of respiration, in groups of hogs have been described by Kelley, Heitman & Morris (60). Under comfortable environmental conditions the prone hog loses about 20 per cent of its heat through conduction. Data are given on heat loss at environmental temperatures of 40° to 100°F. for body weights from 100 to 300 pounds.

The surface area and temperature of that part of the respiratory tract which is related to tidal air flow account for varying parts of heat loss by vaporization. This is admirably illustrated in dairy cattle of the temperate zone, with a deficient ability to sweat [Brody and co-workers (61)]. With rising environmental temperatures from 50° to 105°F., respiration rate increased about fivefold and rectal temperature reached 106°F. The surprising feature was a fall of 30 to 40 per cent in metabolic rate despite the high rectal temperature, which is quite contrary to the reaction in man [DuBois (62)]. A reduction in thyroid activity is suggested as the mechanism involved. It is apparent from the above considerations that the body surface related to heat loss is not the total anatomic surface area, but several overlapping surface areas, whose boundaries have not been well defined.

Recent research on thermoregulator stimuli has been summarized by Lee (63) and by Hardy (64) in their reviews of the field of physiological responses to heat and cold. Studies on man indicate that the hypothalamic center functions to maintain thermal homeostasis by responding to the temperature changes in blood produced by exercise or other metabolic stimuli. The skin receptors protect against environmental stress, both directly and through the central nervous system, by control of blood flow, sweating, and muscular activity. Research on endocrine control of metabolic rate has been noted above. The classical role of the

thyroid and adrenal medulla has been extended to include the anterior pituitary, adrenal cortex, and gonads. Brobeck (65, 66) includes food intake as a mechanism of temperature regulation. In summary, "Thermo-regulation involves many, if not all, other systems in complex fashion" [Lee (63)].

The advances in knowledge of thermo-regulation indicate that thermal homeostasis is essential to warm-blooded mammals in that the integration of the complex systems of receptor and effector mechanisms is pointed toward maintaining the equilibrium between heat production and heat loss. Available information suggests that there is considerable variation among species and individuals in the balance between the various effector responses to both external (environmental) and internal (temperature, chemical, hormonal, and nervous) stimuli. For example, inability to lose heat by sweating under stress of heat stimuli may be balanced by lowered heat production through diminished thyroid activity. The theoretical state of Krogh's true basal metabolism is by definition the condition in which both external and internal stimuli to heat production are *minimal*, and heat production is equivalent to heat loss. Although external stimuli can be adjusted to a minimum with sufficient care, more information is needed about the time required for internal stimuli to reach the minimal level following various degrees of activity. The duration of action of certain internal chemical stimuli has been fairly well established; namely, the S.D.A. after a protein meal lasts about 16 hours (32), but equivalent data for hormonal and nervous activity are lacking. Perhaps a power function of body weight expresses a close approximation to the balance between the effective body surfaces and the internal neuro-endocrine factors. Since heat loss is a surface phenomenon, it appears physiologically sound to pursue the relation of basal metabolism to surface measurements, but this remains as a research goal until the surfaces involved in heat loss noted above can be more accurately defined, with due regard for the basal condition of the internal neuro-endocrine activity.

#### TISSUE METABOLISM

The use of isolated tissues for the study of energy metabolism has become far too comprehensive a subject to be covered in its entirety in a review of this type. A detailed consideration of results obtained with isolated tissues or preparations therefrom is for

example an integral part of recent reviews on biological oxidations (67), protein (68), lipid (69), and carbohydrate (70) metabolism, and phosphorus compounds (71). We shall therefore restrict ourselves here to a discussion of certain general aspects of mammalian tissue metabolism which are emphasized by recent contributions to the literature and which appear to raise points of interest and importance in the field.

*Effect of succinate on tissue metabolism.*—It is well known that practically all mammalian tissues respond to the addition of succinate by an increase in the rate of oxygen consumption. However, it has been repeatedly shown (72, 73) that for most normal tissues, with the possible exception of kidney cortex (73, 74) and heart ventricle (75), the extra oxygen consumption from succinate is due to oxidation of succinate to fumarate and malate only, and that little if any succinate is oxidized beyond this stage. The question then arises as to what effect if any such enhanced oxygen consumption has on normal or depressed respiratory processes, and whether or not the energy produced by the oxidation of succinate to fumarate is available for other metabolic functions of the cell.

A detailed study of these points has recently been made by Furchgott & Shorr (74), who investigated not only the influence of succinate on the respiration of isolated mammalian tissues at both high and low oxygen tensions, but also the effect of succinate oxidation on certain specific metabolic processes known to require oxidative energy for their maintenance, i.e., acetylcholine synthesis in brain, urea synthesis in liver, deamination of amino acids in kidney, and "high energy" phosphate resynthesis in cardiac and smooth muscle. Added succinate at substrate levels (44 mg. per cent) was found to increase the oxygen consumption rate, at both high and low oxygen tensions, for all the tissues studied (brain, liver, heart, skeletal muscle, kidney), but for all tissues except kidney, this stimulation in oxygen consumption was of a transitory nature, disappearing after 60 to 105 min. of incubation, and the total oxygen consumption was even less than that required to oxidize all the succinate present to the stage of fumarate only. Furthermore, the respiratory carbon dioxide output was never increased in the presence of succinate (again except for kidney) and was usually moderately depressed. With kidney, the respiratory data indicated an oxidation of succinate beyond the fumarate stage, in part even to carbon dioxide.

The various energy-requiring processes studied were all depressed at low oxygen tensions without added succinate; in the presence of succinate, oxygen consumption at low oxygen tensions in many instances became equal to or greater than that at high oxygen tensions without succinate; despite this fact, the energy of succinate oxidation was found incapable of increasing the rate of any metabolic process depressed under low oxygen tension. In fact, at a limited concentration of oxygen, the succinate competed with normal substrates for the oxygen present, and thus further depressed the rates of oxidation of normal substrates.

Further evidence on this point is afforded by the data of Barron, Miller & Bartlett (76), who measured for rabbit, cat, and pigeon lung slices not only the increase in oxygen consumption in the presence of added succinate, but also the succinate disappearance. It may be calculated from their data that the extra oxygen consumption in the presence of succinate was either equal to or less than, but in no instance greater than, that required for the oxidation of succinate to the stage of fumarate only.

Important advances in knowledge concerning the effect of succinate on cell metabolism should result from the use of isotope-labeled succinate. Using succinate labeled in the carboxyl group, Olson, Miller, Topper & Stare (75) find, by calculation from the amount of labeled carbon dioxide evolved and on the basis of certain as yet unverified assumptions, that succinate combustion accounts for 50 per cent of the observed oxygen consumption in normal duck heart ventricle slices, indicating that this tissue, as well as kidney, is capable of oxidizing succinate beyond the fumarate stage. The authors point out, however, that present knowledge does not permit a precise estimation of succinate combustion from data obtained with carboxyl-labeled material.

These results emphasize the caution which must be observed in interpreting results obtained with succinate as a substrate. All that is ordinarily measured when succinate is added to a tissue is some function of its succinoxidase activity. It is even doubtful that such measured activity has any quantitative significance since as Rosenthal showed some years ago for liver slices (77), the usual conditions of a tissue metabolism experiment must be considerably modified if succinoxidase activity is to be accurately determined.

These considerations also emphasize the difficulties associated

with a failure to distinguish between respiration and oxygen consumption in the case of isolated tissues. If respiration is defined (78) as "the uptake of gaseous oxygen," then it may be difficult indeed to relate respiration to metabolism, as has been shown; on the other hand, if respiration is regarded in the broader sense as being that aspect of cell metabolism which involves gas exchange, then both oxygen consumption and carbon dioxide production are properly concerned, and oxygen consumption alone may or may not be a true indication of metabolic activity.

*Effect of pH of the medium on tissue metabolism.*—It has generally been assumed that a pH of 7.4 is established for tissue metabolism experiments at 37 to 38° by the use of a medium prepared to contain 0.025 *M* bicarbonate, in equilibrium with a gas phase containing 5 per cent carbon dioxide, and that variation from this pH value, if it occurs, is without significant influence on measured rates of respiration and glycolysis. Recent work indicates that neither of these assumptions is necessarily true.

Bird & Evans (79) report a careful study on the effect of varying the pH of the medium on the anaerobic and aerobic metabolism of rabbit bone marrow. Using a basic Ringer-bicarbonate-glucose medium, variation in pH was accomplished by varying the bicarbonate concentration in the medium and the carbon dioxide tension in the gas phase in equilibrium with the medium; the pH range thus made available was from 6.3 to 7.6. A unique feature of these experiments is that the pH of the medium was determined by exact analysis for bicarbonate content and carbon dioxide tension under the experimental conditions, and not by calculation based on the bicarbonate content of the medium as made up and the carbon dioxide content of the gas mixture used for equilibration, which is the common practice. The authors point out that the latter type of calculation is subject to serious errors, particularly with tissues which exhibit a moderate or high aerobic or anaerobic glycolytic rate, since in the necessary preliminary equilibration period between tissue and medium, almost half of the bicarbonate initially present may be decomposed by acid formation.

Measurements were made of oxygen consumption, R.Q., aerobic and anaerobic acid production, glucose utilization, and lactic acid production, under both aerobic and anaerobic conditions, in media ranging in pH from 6.3 to 7.6. It was found that both oxygen

consumption and R.Q. were relatively unaffected by change in pH over the range indicated; by contrast, both aerobic and anaerobic glycolysis were markedly influenced by the pH of the medium, aerobic glycolysis being maximal at pH 7.2, and both aerobic and anaerobic glycolysis showing a sharp and substantially linear decrease in rate with decrease in pH. In the lower pH range, aerobic glycolysis was about one-half and anaerobic glycolysis about one-fifth of the value obtained at pH 7.2 to 7.4. Glucose utilization paralleled lactic acid formation anaerobically and accounted for both lactic acid production and oxygen consumption aerobically.

These results on glycolysis, along with similar ones reported recently for the lymphosarcoma cell (80), and earlier for retina (81), brain (82), and diaphragm (83), serve to re-emphasize the importance of pH in the glycolytic processes and indicate the need for a further careful study of this factor. They would also appear to throw into some question the comparative quantitative validity of the many values for aerobic and anaerobic glycolysis in the literature.

Furthermore, as Bird & Evans (79) point out, they indicate that any attempt to relate respiration and glycolysis in a quantitative way as a means of characterizing a tissue metabolically is open to question unless the effect of pH is established or controlled. Such attempted relation between respiration and glycolysis, or between aerobic and anaerobic glycolysis, is of course the basis for the various "derived quotients" ("Meyerhof oxidation quotient," "fermentation excess," etc.) which have been used by some [see Burk (84) for details] as a basis for comparing the metabolism of normal and tumor tissue. If aerobic and anaerobic glycolysis rates can be varied widely and to a different extent merely by change in pH, without any corresponding change in the rate of oxygen consumption, certainly the quantitative significance of any relation between these various rates becomes obscure, at least on the basis of present data, and it even becomes doubtful that there is any direct connection between them.

Elliott & Birmingham (85), studying the effect of the pH of the medium on the respiration of brain tissue, find the optimal pH higher for slices (8.0 to 9.3) than for suspensions (7.0 to 8.0). They attribute this difference to the possibility that the pH within a tissue slice may be maintained at a lower value than that of the

surrounding medium. They find that a glass electrode after five minutes' contact with a brain slice gives a significantly lower pH value than is obtained for the medium, and they attribute this to a lower pH within the slice. It appears more likely that they were measuring the pH of a thin layer of medium, confined between the slice and the electrode and accumulating metabolically generated carbon dioxide and lactic acid.

*Liberation of intracellular enzymes.*—One of the difficulties associated with the use of tissue homogenates in metabolism studies which is not encountered with slices or coarse minces is the influence which the liberation of intracellular enzymes may have on experimental results. The intracellular enzymes which are of well-known importance in this connection include adenosinetriphosphatase and diphosphopyridine nucleotidase; the latter is now known to consist of at least two enzymes, one of which liberates (and is inhibited by) nicotinamide and is thus a nucleosidase, while the other splits the pyrophosphate linkage of diphosphopyridine nucleotide (DPN) (86) and is not inhibited by nicotinamide. Recently a proteinase has been added to the list of intracellular enzymes which influence metabolism in tissue homogenates, and other enzymes doubtless remain to be discovered.

An example of the significance of diphosphopyridine nucleotidase activity in the interpretation of results with tissue homogenates is given by the recent studies of Larner, Jandorf & Summerson (87) on the requirement for DPN in aerobic pyruvate metabolism by brain tissue. They find that the limiting factor in demonstrating a need for DPN under these conditions is primarily the degree of subdivision of the tissue. Thoroughly homogenized brain tissue (fine homogenates) does not utilize pyruvate aerobically unless DPN is added, along with various other co-factors, or unless endogenous DPN is prevented from destruction during the homogenization. Less well ground tissue (coarse homogenates) on the other hand does not require added DPN. The authors show that these differences are due to the liberation and activation of intracellular diphosphopyridine nucleotidase by thorough homogenization, with consequent destruction of the DPN originally present; in coarse homogenates, cell destruction is not sufficiently extensive to release active diphosphopyridine nucleotidase, and added DPN is unnecessary. Characterization of homogenates as either coarse or fine is regarded as arbitrary and unsatisfactory,

but no more adequate criteria appear to be available at present; the possible use of diphosphopyridine nucleotidase activity in this connection is suggested.

Barron, Miller & Bartlett (76) attribute the pronounced decrease in rate of oxygen consumption for rat lung homogenates as compared to lung slices in large part to the release of intracellular nucleosidase (diphosphopyridine nucleotidase). Lung tissue was found to show the greatest diphosphopyridine nucleotidase activity after homogenization of the various rat tissues studied; on a relative basis (lung as 100) the activities of various other rat tissues were as follows: intestine, 63; brain, 33; liver, 28; heart, 22; kidney, 15. No activity was found for skin, testis, or blood.

Although the method of measurement of diphosphopyridine nucleotidase activity used by Barron *et al.* appears to be an improvement over previous methods, it does not distinguish between nucleosidase and pyrophosphatase activities, and no proof is offered that the results for any tissue represent maximal or true diphosphopyridine nucleotidase activity; the extent of homogenization would appear to enter in here, as discussed above, along with enzyme activation and stability. It is pointed out that release of diphosphopyridine nucleotidase in lung tissue may play a role in the mechanism of action of lung irritants, a suggestion which deserves further exploration.

Other recent examples of the relation of diphosphopyridine nucleotidase activity to results obtained with tissue suspensions include the demonstration that added DPN is necessary to restore the ability of minced liver to inactivate  $\alpha$ -estradiol (88) and testosterone (89).

An interesting and important recent development in the field of intracellular enzymes is the demonstration by Krinsky & Racker (90) that homogenization of mouse brain liberates an intracellular proteinase which acts upon the proteins of the enzymes glyceraldehyde phosphate dehydrogenase and phosphofructokinase, in the first instance to produce a marked inhibition of brain glycolysis. This proteinase is activated by ferrous ions in the presence of either cysteine or ascorbic acid; thus activation of the proteinase accounts for the inhibitory effect of ferrous ions on brain glycolysis in homogenates. Addition of glyceraldehyde phosphate dehydrogenase to brain preparations inhibited by either ferrous iron or action of proteolytic enzymes restores activity (91).

The proteinase is similar in its behavior to a cathepsin. Action of the proteinase may be overcome by the presence of added amides and esters of amino acids, of which phenylglycine ethyl ester is the most effective—this effect is probably analogous to the protective action of nicotinamide against diphosphopyridine nucleotidase activity in brain homogenates.

*Distribution of metabolic activity within the cell.*—A recent development in the study of cell metabolism which promises to be of growing significance is the localization of certain types of metabolic activity in various subcellular fractions of the cell. It was shown a few years ago (92) that mechanically disrupted cells suspended in isotonic saline could be separated by centrifugation at various speeds into four broad fractions: a heavy fraction consisting mainly of nuclei; a "large granule" fraction, thought to represent mitochondria for the most part; a small particle or "microsome" fraction consisting of insoluble submicroscopic particles; and a "soluble fraction" or supernatant fluid. Study of the distribution of cytochrome oxidase and succinoxidase activity among the various fractions (92, 93) revealed that these enzymatic activities were associated, probably exclusively, with the "large granule" fraction, thus placing on a systematic basis earlier and scattered observations (Warburg, Barron, Stern) regarding the metabolic activity of insoluble components of the cell.

The "large granule" fraction isolated from cell homogenates prepared in either water or isotonic salt solution, although presumably representing the mitochondria of the cell, does not show either the morphological or staining characteristics of true mitochondria. Hogeboom, Schneider & Pallade (94) have recently found that homogenization in hypertonic sucrose solution (0.8 to 1.0 *M*) yields after differential centrifugation "large granules" free from other cellular components which closely resemble intact mitochondria in morphology and response to staining.

Detailed studies on the enzymatic capabilities of rat liver mitochondria isolated as described above have been reported by Kennedy & Lehninger (95), who find that this fraction of the cell contains all the measurable activity of the original tissue in the oxidation of fatty acids (octanoic acid was used), provided the necessary co-factors ( $Mg^{++}$ , neutral salt or sucrose, ATP, cytochrome-*c*, and catalytic amounts of malate) are added. In the presence of added adenosinetriphosphate, cytochrome-*c*,  $Mg^{++}$ ,

and inorganic phosphate, mitochondria also promote the aerobic oxidation of citrate,  $\alpha$ -ketoglutarate, and pyruvate plus oxaloacetate, reactions which are well-known steps in the Krebs tricarboxylic acid cycle. They likewise catalyze the condensation of oxaloacetate and pyruvate to yield citrate. Use of isotope-labeled inorganic phosphate showed that oxidations promoted by mitochondria were associated with significant esterification of inorganic phosphate, in the oxidation of both Krebs cycle intermediates and octanoic acid; there is also a significant incorporation of inorganic phosphate into the phospholipid and pentose nucleic acid components of the mitochondria themselves, as well as into an unidentified "phosphoprotein" fraction, during aerobic oxidation of Krebs cycle components (96).

The metabolic activity of liver mitochondria in the oxidation of fatty acid has been confirmed by Schneider (97), who however reports more activity in preparations from isotonic than from hypertonic sucrose solution; this may be due to the absence from Schneider's preparations of added malate, or possibly to osmotic damage (95). Schneider & Potter (98) have studied the distribution in rat liver and kidney fractions, prepared from isotonic sucrose solution, of the "oxaloacetic acid oxidase system," an as yet ill-defined enzyme complex required for the oxidation of oxaloacetic acid and believed to involve "most if not all of the enzymes of the Krebs cycle." They find that while the mitochondrial fraction has the highest activity of the various fractions, it contains less than half the total activity of the original tissue. When the various fractions are recombined, the total activity in the case of liver is greater than that of the original homogenate, while for kidney it is much less. Evidence is presented indicating the existence of a labile accessory factor in kidney preparations, loss of which is presumably responsible for the low results with recombined fractions from this tissue. These results appear to invalidate Schneider's postulate (99) that the total activity of the combined fractions must closely approximate that of the original material, a requirement which implies that the various fractions are either autonomous or related to one another in a stable and reproducible way, neither of which is necessarily true; and they also indicate the need for a more careful study of the interrelationship between the various fractions, as indeed further work (98, 102) has stressed.

The submicroscopic or microsome fractions of rat liver and

kidney appear to possess little or no oxidative activity, although the fraction from rat kidney markedly inhibits oxaloacetic oxidase activity of kidney mitochondria (98). In the special case of the Harding-Passey mouse melanoma, Lerner, Fitzpatrick, Calkins & Summerson (100) have shown that the tyrosinase and dihydroxyphenylalanine (DOPA) oxidase activities of this tissue, previously thought to be separable by procedures applicable to soluble enzymes (101), are in fact inseparably associated with submicroscopic insoluble cell particles of the nature of microsomes. Furthermore, the evidence indicates that DOPA is not necessarily a substrate in the enzymatic formation of melanin by these particles, but rather plays the part of an essential co-factor in the aerobic oxidation of tyrosine.

In contrast to the localization of oxidative activity of the cell in the insoluble particulate components, glycolytic activity appears to be primarily a function of the soluble phase of the cell. Le Page & Schneider (102) find that only the soluble fraction of rabbit liver and Flexner-Jobling rat carcinoma tissue retains any marked ability to promote the anaerobic formation of lactic acid from glucose under optimal conditions, although some interrelation between the soluble and insoluble cell fractions is shown by the finding that the concomitant presence of nuclear, mitochondrial, or submicroscopic fractions, separately or together, enhanced the glycolytic power of the soluble fraction. For rat liver, combined aldolase, triosephosphate dehydrogenase and lactic dehydrogenase activities have been found (95) to be almost completely absent from the nuclear and mitochondrial fractions.

These results are in agreement with the well-known fact that a number of the enzymes concerned in the glycolytic process have been isolated as water-soluble proteins, while there is a striking lack of success along these lines in connection with the oxidative enzymes of the cell. The separation and characterization of the oxidative enzymes of the insoluble particulate components of the cell appears to offer a major challenge to those who are exploring the metabolism of living tissue at the intracellular level.

#### LITERATURE CITED

1. PROUTY, L. R., *Federation Proc.*, **8**, 128-29 (1949)
2. PROUTY, L. R., BARRETT, M. J., AND HARDY, J. D., *Rev. Sci. Instruments*, **20**, 357 (1949)
3. BRODY, S., *Missouri Agr. Expt. Sta. Research Bull.*, No. 423, 1-43 (1948)
4. KLEIBER, M., *Physiol. Revs.*, **27**, 511-41 (1947)

5. BRODY, S., *Bioenergetics and Growth*, 1023 pp. (Reinhold Publishing Corp., New York, 1945)
6. GALVÃO, P. E., *Am. J. Physiol.*, **148**, 478-89 (1947)
7. ADOLPH, E. F., *Science*, **109**, 579-85 (1949)
8. KEYS, A., *Federation Proc.*, **8**, 523-29 (1949)
9. THOMPSON, E. M., COX, E. W., AND RIDGWAY, A. M., *J. Nutrition*, **36**, 507-17 (1948)
10. HARDY, J. D., MILHORAT, A. T., AND DUBOIS, E. F., *J. Nutrition*, **21**, 383-404 (1941)
11. GALVÃO, P. E., *J. Applied Physiol.*, **1**, 385-94 (1948)
12. GALVÃO, P. E., *J. Applied Physiol.*, **1**, 395-401 (1948)
13. ORSINI, D., *Arquiv. brasil. nutrição*, **3**(5), 6-36 (6), 6-65 (1947)
14. KALLER, H., AND RELLER, E., *Klin. Wochschr.*, **24**/25, 682-84 (1946-47)
15. MARSTON, H. R., *Australian J. Sci. Research [B]* No. 1, 93-129 (1948)
16. BRODY, S., COMFORT, J. E., KIBLER, H. H., AND WORSTELL, D. M., *Missouri Agr. Expt. Sta. Research Bull.*, No. 404, 1-16 (1947)
17. KIBLER, H. H., AND BRODY, S., *Missouri Agr. Expt. Sta. Research Bull.*, No. 438, 1-22 (1949)
18. MORRISON, P. R., *J. Cellular Comp. Physiol.*, **31**, 281-91 (1948)
19. MORRISON, P. R., *J. Cellular Comp. Physiol.*, **31**, 69-96 (1948)
20. HEILESEN, B., *Acta Physiol. Scand.*, **13**, 181-95 (1947)
21. TAYLOR, C. M., LAMB, M. W., ROBERTSON, M. E., AND MACLEOD, G., *J. Nutrition*, **35**, 511-21 (1948)
22. TAYLOR, C. M., PYE, O. F., AND CALDWELL, A. B., *J. Nutrition*, **36**, 123-31 (1948)
23. TAYLOR, C. M., PYE, O. F., CALDWELL, A. B., AND SOSTMAN, E. R., *J. Nutrition*, **38**, 1-10 (1949)
24. BERG, W. E., *Am. J. Physiol.*, **149**, 597-610 (1947)
25. BERG, W. E., *Am. J. Physiol.*, **152**, 465-69 (1948)
26. SADHU, D. P., *Missouri Ag. Expt. Sta. Research Bull.*, No. 408, 1-64 (1947)
27. SADHU, D. P., AND BRODY, S., *Am. J. Physiol.*, **149**, 400-3 (1947)
28. SADHU, D. P., AND BRODY, S., *Am. J. Physiol.*, **151**, 130-33 (1947)
29. SADHU, D. P., AND BRODY, S., *Am. J. Physiol.*, **151**, 342-44 (1947)
30. BARKER, S. B., *Ann. Rev. Physiol.*, **11**, 45-82 (1949)
31. ANDERSON, J. T., AND NASSET, E. S., *J. Nutrition*, **36**, 703-20 (1948)
32. GLICKMAN, N., MITCHELL, H. H., LAMBERT, E. H., AND KEETON, R. W., *J. Nutrition*, **36**, 41-57 (1948)
33. DEUEL, H. J., JR., MESERVE, E. R., STRAUB, E., HENDRICK, C., AND SCHEER, B. T., *J. Nutrition*, **33**, 569-82 (1947)
34. SCHEER, B. T., SOULE, D. F., FIELDS, M., AND DEUEL, H. J., JR., *J. Nutrition*, **33**, 583-92 (1947)
35. SCHEER, B. T., CODIE, J. F., AND DEUEL, H. J., JR., *J. Nutrition*, **33**, 641-48 (1947)
36. SCHEER, B. T., STRAUB, E., FIELDS, M., MESERVE, E. R., HENDRICK, C., AND DEUEL, H. J., JR., *J. Nutrition*, **34**, 581-86 (1947)
37. FRENCH, C. E., BLACK, A., AND SWIFT, R. W., *J. Nutrition*, **35**, 83-88 (1948)
38. BLACK, A., FRENCH, C. E., AND SWIFT, R. W., *J. Nutrition*, **37**, 275-88 (1949)

39. BLACK, A., FRENCH, C. E., COWAN, R. L., AND SWIFT, R. W., *J. Nutrition*, **37**, 289-301 (1949)
40. LUNDBAEK, K., *Yale J. Biol. Med.*, **20**, 533 (1948)
41. SAMUELS, L. T., GILMORE, R. C., AND REINECKE, R. M., *J. Nutrition*, **36**, 639-51 (1948)
42. BEATTIE, J., AND HERBERT, P. H., *Brit. J. Nutrition*, **1**, 185-91 (1947)
43. BEATTIE, J., AND HERBERT, P. H., *Brit. J. Nutrition*, **1**, 192-202 (1947)
44. BENDITT, E. P., HUMPHREYS, E. M., WISSLER, R. W., STEFFEE, C. H., FRAZIER, L. E., AND CANNON, P. R., *J. Lab. Clin. Med.*, **33**, 257-68 (1948)
45. BENDITT, E. P., WOOLRIDGE, R. L., AND STEPTO, R., *J. Lab. Clin. Med.*, **33**, 269-79 (1948)
46. BOSSHARDT, D. K., PAUL, W. J., O'DOHERTY, K., AND BARNES, R. H., *J. Nutrition*, **36**, 773-83 (1948)
47. DEUEL, H. J., JR., in M. Sahyun's *Proteins and Amino Acids in Nutrition*, 540 pp. (Reinhold Publishing Corp., New York, 1948)
48. WHITE, H. L., HEINBECKER, P., AND ROLF, D., *Am. J. Physiol.*, **151**, 239-44 (1947)
49. BRATZLER, J. W., BARNES, J. R., AND SWIFT, R. W., *J. Nutrition*, **38**, 41-50 (1949)
50. MUKHERJEE, R., AND MITCHELL, H. H., *J. Nutrition*, **37**, 303-15 (1949)
51. HAWLEY, E. E., MURLIN, J. R., NASSET, E. S., AND SZYMANSKI, T. A., *J. Nutrition*, **36**, 153-69 (1948)
52. HOFFMANN, F., HOFFMANN, E. J., AND TALESNIK, J., *J. Physiol.*, **107**, 251-64 (1948)
53. WHITCHER, C. E., AND GRIFFITH, F. R., JR., *Am. J. Physiol.*, **156**, 114-16 (1949)
54. HARDY, J. D., SHORR, E., AND DUBOIS, E. F., *Federation Proc.*, **6**, 122 (1947)
55. QUIMBY, F. H., PHILLIPS, N. E., AND WHITE, I. U., *Am. J. Physiol.*, **154**, 188-92 (1948)
56. QUIMBY, F. H., *Endocrinology*, **42**, 263-72 (1948)
57. MACHLE, W., AND HATCH, T. F., *Physiol. Revs.*, **27**, 200-27 (1947)
58. HARDY, J. D., AND DUBOIS, E. F., *J. Nutrition*, **15**, 461-75 (1938)
59. HERTZMAN, A. B., AND RANDALL, W. C., *Federation Proc.*, **8**, 74 (1949)
60. KELLY, C. F., HEITMAN, H., JR., AND MORRIS, J. R., *Agr. Eng.*, **29**, 525-29 (1948)
61. KIBLER, H. H., BRODY, S., AND WORSTELL, D. M., *Missouri Agr. Expt. Sta. Research Bull.*, No. 435, 1-32 (1949)
62. DUBOIS, E. F., *Fever and the Regulation of Body Temperature*, 68 pp. (Charles C Thomas, Springfield, Illinois, 1948)
63. LEE, D. H. K., *Ann. Rev. Physiol.*, **10**, 365-86 (1948)
64. HARDY, J. D., *Ann. Rev. Physiol.* (In press)
65. BROBECK, J. R., *Yale J. Biol. Med.*, **20**, 545 (1948)
66. BROBECK, J. R., *Ann. Rev. Physiol.*, **10**, 315-28 (1948)
67. PREISLER, P. W., AND HUNTER, F. E., JR., *Ann. Rev. Biochem.*, **18**, 1-34 (1949)
68. NEUBERGER, A., *Ann. Rev. Biochem.*, **18**, 243-66 (1949)
69. LEHNINGER, A. L., *Ann. Rev. Biochem.*, **18**, 191-216 (1949)
70. WOOD, H. G., AND LORBER, V., *Ann. Rev. Biochem.*, **18**, 299-334 (1949)

71. LIPMANN, F., AND KAPLAN, N. O., *Ann. Rev. Biochem.*, **18**, 267-98 (1949)
72. QUASTEL, J. H., AND WHEATLEY, A. H. M., *Biochem. J.*, **26**, 725 (1932)
73. ELLIOTT, K. A. C., GREIG, M. A., AND BENOY, M. P., *Biochem. J.*, **31**, 1003-20 (1937)
74. FURCHGOTT, R. F., AND SHORR, E., *J. Biol. Chem.*, **175**, 201-15 (1948)
75. OLSON, R. E., MILLER, O. N., TOPPER, Y. J., AND STARE, F. J., *J. Biol. Chem.*, **175**, 503-14 (1948)
76. BARRON, E. S. G., MILLER, Z. B., AND BARTLETT, G. R., *J. Biol. Chem.*, **171**, 791-800 (1947)
77. ROSENTHAL, O., *Biochem. J.*, **31**, 1710-18 (1937)
78. UMBREIT, W. W., BURRIS, R. H., AND STAUFFER, J. F., *Manometric Techniques and Related Methods for the Study of Tissue Metabolism*, 198 pp. (Burgess Publishing Co., Minneapolis, 1945)
79. BIRD, R. M., AND EVANS, J. D., *J. Biol. Chem.*, **178**, 289-300 (1949)
80. SUMMERSON, W. H., GILDER, H., AND LEE, J. M., *Federation Proc.*, **7**, 194 (1948)
81. CRAIG, F. N., AND BEECHER, H. K., *J. Gen. Physiol.*, **26**, 473-78 (1943)
82. CRAIG, F. N., *J. Gen. Physiol.*, **27**, 325-38 (1944)
83. STADIE, W. C., AND ZAPP, J. A., JR., *J. Biol. Chem.*, **170**, 55-65 (1947)
84. BURK, D., *Cold Spring Harbor Symposia Quant. Biol.*, **7**, 420-59 (1939)
85. ELLIOTT, K. A. C., AND BIRMINGHAM, M. K., *J. Biol. Chem.*, **177**, 51-58 (1949)
86. KORNBERG, A., AND LINDBERG, O., *J. Biol. Chem.*, **176**, 665-78 (1948)
87. LARNER, J., JANDORF, B. J., AND SUMMERSON, W. H., *J. Biol. Chem.*, **178**, 373-82 (1949)
88. COPPEDGE, R. L., SEGALOFF, A., SARETT, H. P., AND ALTSCHUL, A. M., *J. Biol. Chem.*, **173**, 431-32 (1948)
89. SWEAT, M. L., AND SAMUELS, L. T., *J. Biol. Chem.*, **175**, 1-5 (1948)
90. KRIMSKY, I., AND RACKER, E., *J. Biol. Chem.*, **179**, 903-14 (1949)
91. RACKER, E., AND KRIMSKY, I., *J. Biol. Chem.*, **173**, 519-33 (1948)
92. HOGEBOOM, G. H., CLAUDE, A., AND HOTCHKISS, R. D., *J. Biol. Chem.*, **165**, 615-19 (1946)
93. SCHNEIDER, W. C., CLAUDE, A., AND HOGEBOOM, G. H., *J. Biol. Chem.*, **172**, 451-58 (1948)
94. HOGEBOOM, G. H., SCHNEIDER, W. C., AND PALLADE, G. E., *J. Biol. Chem.*, **172**, 619-35 (1948)
95. KENNEDY, E. P., AND LEHNINGER, A. L., *J. Biol. Chem.*, **179**, 957-72 (1949)
96. FRIEDKIN, M., AND LEHNINGER, A. L., *J. Biol. Chem.*, **177**, 775-88 (1949)
97. SCHNEIDER, W. C., *J. Biol. Chem.*, **176**, 259-66 (1948)
98. SCHNEIDER, W. C., AND POTTER, V. R., *J. Biol. Chem.*, **177**, 893-903 (1949)
99. SCHNEIDER, W. C., *J. Biol. Chem.*, **165**, 585-93 (1946)
100. LERNER, A. B., FITZPATRICK, T., CALKINS, E., AND SUMMERSON, W. H., *J. Biol. Chem.*, **178**, 185-95 (1949)
101. HOGEBOOM, G. H., AND ADAMS, M. H., *J. Biol. Chem.*, **145**, 273-79 (1942)
102. LE PAGE, G. A., AND SCHNEIDER, W. C., *J. Biol. Chem.*, **176**, 1021-27 (1948)
103. LUSK, G., *The Elements of the Science of Nutrition*, 4th Ed., 844 pp. (W. B. Saunders Co., Philadelphia, 1928)
104. KUNDE, M. M., AND STEINHAUS, A. H., *Am. J. Physiol.*, **78**, 127-35 (1926)

## THE PERIPHERAL CIRCULATION<sup>1</sup>

By O. G. EDHOLM

*Department of Physiology, University of Western Ontario, London, Canada*

There is a very considerable literature concerned with the circulation, apart from purely physiological papers. Many articles which are essentially clinical contain valuable physiological data. The problem of selection of these papers is difficult, and many references are omitted. In addition, it is evident that important papers may have been overlooked, particularly among the foreign journals, some of which were received too late for inclusion in this review. The reviewer's apologies are due to authors for these omissions.

Ogden (1) has reviewed the organization of cardiovascular function. Marvin (2), in a review of recent advances in cardiovascular disease, deals with many physiological aspects of the circulation. Other reviews will be mentioned under the appropriate headings.

### TECHNIQUES

The measurement of arterial pressure, particularly in man, has been considerably improved by the introduction of new techniques. The Lilly capacitance manometer has been applied in human work by Peterson *et al.* (3, 4), using an improved amplifier (5). Lambert & Jones (6) have described a resistance wire manometer which can be used in conjunction with intravascular catheters. Marsh (7, 8) has modified the Lambert-Wood strain gauge manometer to measure mean pressures and used it successfully in rats. Friedman & Freed (9) have used an amplifier in conjunction with a cuff on the tail to measure arterial pressure in rats. Segers & Hendricky (10) record the digital pulse and electrocardiogram simultaneously, giving a convenient measurement of pulse wave velocity. Schlapp & Walker (11) have used a similar technique. An ink-writing cardiograph has been described which gives a graphic recording of heart rate intervals (12). Curtis & Nickerson (13) have applied the transducer tube to the recording of peripheral pulses. Goodyer (14) has given a brief description of an impedance plethysmograph. The Lewis-Grant plethysmograph has been adapted for use in a

<sup>1</sup> This review covers the period from July 1948 to June 1949.

pressure chamber by Kerslake (15). Greenfield (16) has constructed an ingenious plethysmograph, enclosing the whole fetus, for measuring the rate of blood flow in the umbilical vessels. A useful glue for sealing plethysmographs is described (17). The thermostromuhr has been discussed by Probst & Fleisch (18) and by Cerletti & Rothlin (19), the latter obtaining excellent results using models. Moe (20) has devised a membrane differential manometer recording blood flow graphically. A bubble flow meter for measuring venous flow has been developed by Selkurt (21). The strain gauge manometer has been used by Pollack & Wood to measure venous pressure in man (22). Kay *et al.* (23) have used the electrokymograph to measure changes in diameter of the aorta and pulmonary artery. They conclude that it is a useful, but not a completely quantitative, technique. A thermal flow meter for measurement of blood flow in the colon has been described in a preliminary note by Scarborough *et al.* (24). A method for obtaining portal blood samples over a long period of time is described by Cresson & Glenn (25). McDowall (26) has briefly described a simple model of the circulation.

#### HAEMODYNAMICS

Lamport (27) has developed the law relating blood flow to perfusion pressure. Burton (28) finds a linear relationship between pressure and flow in the perfused frog's leg. Flow ceases at a pressure of 5 cm. saline, due to residual tension, part of which may be due to interfacial tension. Williams & Schroeder (29) have devised a new method for measuring peripheral resistance, recording the curve of intra-arterial pressure below the point of sudden occlusion of a major artery, or asystolic pressure gradient. Although this gradient is a measure of both elasticity and resistance, the last is the major factor. The haemodynamics of aortic occlusion have been studied by van Harreveld *et al.* (30). They reach the interesting conclusion that peripheral resistance should be regarded as a regulator of blood flow rather than a primary determinant of blood pressure. Müller (31) has studied the pressure drop in small blood vessels, especially in capillaries. Timm (32) has recorded the blood flow in the aorta, using thorotrast and contrast oil drops with rapid x-ray cinematography. The flow in the aorta is laminar during systole, with turbulent flow in the sinus of Valsalva. There was no evidence of turbulent flow in the descending aorta or at the origin of branches.

A study by Mendlowitz (33) on the effect of changes in the red cell count on digital intravascular viscosity shows that in anaemia there is only a slight decrease in viscosity. In polycythaemia, the viscosity is considerably increased, i.e., with a haematocrit of 73, the viscosity appears to be 169 per cent of the normal.

#### ARTERIAL PRESSURE

Kean & Hammill (34) have collected together records of arterial pressure measurements in different races, showing that in some there is no tendency for blood pressure to increase with age. An analysis by Gover (35) of the blood pressure in 11,490 members of low income farm families reveals the startling fact that the average blood pressure in the age groups over 55 would be classed as hypertensive. Nieuwmeijer & Brandsma (36) have recorded the blood pressure in a group of factory workers during the war in Holland. The blood pressure and haemoglobin levels in Olympic athletes showed some differences between subjects from tropical as compared to those from temperate climates (37). Thomson & Doupe (38) have compared direct readings of intra-arterial pressure in man with sphygmomanometer measurements. The results show a wide range of divergence, with no consistent systematic errors. These findings make it clear that sphygmomanometer readings can only be used with considerable caution in any work demanding accuracy.

In the age group 10 to 17 there was little variation in the level of diastolic arterial pressure. The response to exercise in this group was carefully studied (39). Boynton & Todd (40) have examined the relationship between arterial pressure and body weight in over 75,000 university students. Systolic arterial pressure increases with weight in all the age groups from 24 to 41, but the increase in diastolic pressure is less significant. In cases with a family history of hypertension there was a slightly higher mean systolic pressure in both men and women. Matthes & Ebeling (41) have studied the variation of arterial pressure and heart rate with respiration. Heart rate, measured with a cardiometer, shows a mirror image of arterial pressure. The mean arterial pressure in unanaesthetized dogs is significantly higher in males than females (42).

#### EXERCISE

In athletes there appears to be a greater degree of vasodilata-

tion in muscle vessels when work is done for which the individual is trained. On cessation of exercise there is a marked fall of arterial pressure, which is abolished by the inhalation of carbon dioxide (43). The return of the heart rate to pre-exercise levels is accelerated by bandaging the limbs firmly (44).

#### VASOMOTOR CONTROL OF THE CIRCULATION

Transcortical stimulation of the orbital surface of the frontal lobe raised the arterial pressure in five out of eight patients (45). Arterial pressure effects can be elicited by stimulation of the frontal lobe and motor cortex. Posterior to this pressor area, depressor effects are obtained (46). Mecholyl applied to the pressor area causes a profound fall of arterial pressure (47). Stimulation of the orbital and mesial surface of the cerebral cortex in the cat for one to two hours produces vasoconstriction in the renal cortex (48). Heymans & Pannier (49) have demonstrated the predominance of the bulbar vasomotor centre over the spinal centres in the intact animal. Leusen (50, 51) has studied the effects of various ions on the vasomotor centre. Increased concentration of potassium raises blood pressure, whereas magnesium lowers arterial pressure and diminishes the vasomotor reflexes. Neil, Redwood & Schweitzer (52) have studied the effects of electrical stimulation of the carotid sinus and aortic nerves. The effects vary with different forms of stimuli, and in the species studied, but the most striking result was the effect of increasing the depth of anaesthesia with chloralose in the cat; this converted depressor responses to pressor. Similar results are independently reported by Douglas, Innes & Kosterlitz (53, 54). This is the first definite evidence of pressor impulses from the carotid sinus. Sigler (55) gives a comprehensive account of the effects of pressure on the carotid sinus in a large series of patients. Rosenberg (56) has demonstrated both temporal and spatial summation of vasodilator reflexes elicited by stimulation of the aortic nerves. Jarisch & Zotterman (57) have described depressor reflexes arising from nerve endings at the orifice of the caval veins, and the surface of the pulmonary veins. Chatonnet & Vial (58) have followed the changes in arterial pressure in the rat during progressive ascending destruction of the spinal cord. Arterial pressure does not change significantly until the level of the fourth thoracic segment is reached, when there is a sharp fall of arterial pressure, increasing

as destruction is extended up to the first thoracic segment. There is subsequently a gradual recovery of arterial pressure if the animal survives for several days. Sarnoff, Hardenbergh & Whittenberger (59) have studied the arterial pressure response to the Valsalva test in dogs. The overshoot of arterial pressure at the termination of the test is increased by vagotomy and abolished by ascending spinal anaesthesia. Autio *et al.* (60) have followed heart rate changes in the Valsalva test. Folkow & Uvnäs and their colleagues have studied the vasomotor supply to peripheral vessels in the cat (61, 62, 63) and dog (64, 65). Vasoconstrictor impulses to the hind limb and splanchnic region in the cat appear to be mediated by norepinephrine, and vasodilator impulses to the muscle blood vessels are cholinergic. In the dog, vasoconstrictors also appear to liberate norepinephrine. No evidence was obtained of vasodilators supplying blood vessels in the skin. Arnott *et al.* (66) could not find any evidence of cutaneous vasodilators in man.

Binet & Burstein, in a series of brief communications (67 to 73), describe reactions studied in a preparation consisting of a hind limb, isolated from the rest of the circulation, but with the nerve supply intact, and perfused with the animal's own blood at a constant rate (74). On carotid artery occlusion there is a marked constriction in the hind limb, followed by a dilatation on the release of the occlusion (67). During the fall of arterial pressure induced by vagal stimulation, there is vasoconstriction, with vasodilatation during the overshoot of arterial pressure when stimulation is stopped. Denervation abolishes the first effect, and the second effect is replaced by vasoconstriction, possibly due to epinephrine (68). There is strong vasoconstriction when the sympathetic chain is stimulated. Dilator effects are difficult to display and are best shown in the reflex dilatation when arterial pressure in the main circulation is raised with epinephrine (69). Changes in carbon dioxide tension in perfusing blood has little effect on the blood vessels in the limb (70). Sodium chloride from 1 to 4 per cent solution has either no effect or produces a very feeble dilatation (71); although Walcott & Deyrup (75) obtained a marked, if transient fall in arterial pressure when 5 to 20 per cent sodium chloride was given intravenously to the whole animal, due in part to a peripheral vasodilatation. Potassium produces vasodilatation, as cobalt does, whereas calcium and magnesium have no effect. During muscular

contraction there is a fall of pressure in the perfused limb, and this dilatation is unaffected by antihistamine drugs (72). Stopping the perfusion for 5 to 10 sec. produces a marked fall of pressure which returns to normal 30 to 50 sec. after perfusion is restored (73). In cross circulation experiments, Malmejac & Chardon (76) found that raising the arterial pressure in the donor dog caused vasoconstriction in the perfused hind limb with dilatation on lowering pressure. Siems & Kosman (77) compared the effects of ventral root section, combined dorsal and ventral root section, and peripheral nerve section on the circulation in the hind limb of dogs. Three months after operation there was no significant difference in the rate of blood flow in animals with root sections and controls, but in animals with peripheral nerve section there was a significant reduction. Barcroft & Walker (78) have followed hand blood flow before and immediately after sympathectomy. There is an immediate increase in blood flow after operation, the maximal being attained within 24 hr. Thereafter the flow declines rapidly and reaches approximately preoperative level in two weeks. No difference was observed between the effects of ganglionectomy and preganglionic section. Similar findings are reported by Hoobler *et al.* (267). For the first six months after sympathectomy, Barcroft & Hamilton (79, 80) found there was complete absence of vasomotor and sudomotor responses in the hand. After nine months, in the majority of cases there is some return of either vasomotor or sudomotor reflexes, or both, strongly suggesting regeneration of autonomic fibres.

Millen (81) has examined the innervation of small blood vessels, describing three plexus in the walls of small arteries; in arterioles, nerve fibres ran parallel to the vessels. Single beaded fibres accompany the capillaries, but no endings could be seen on the walls.

#### THE EFFECT OF GRAVITY

Green, Iglauer & McGuire (82, 83) have recorded arterial pressure changes in the brachial artery during tilting from head up to head down. Arterial pressure rises immediately and gradually falls during the 15 sec. the subjects were kept in this position. On returning to the original position, the pressure falls below control levels, gradually returning to normal. In hypertensive subjects, four groups were distinguished, with normal, increased, decreased, or delayed responses. Horvath & Botelho (84) find that the fall of

blood pressure in the upright position is increased after hot baths and slightly diminished after a cold bath. The fall of arterial pressure that occurs on prolonged passive tilting into the upright position is greatly reduced by faradic stimulation of the muscle groups in the thigh and calf at the rate of 18 per min., and the leg-tongue circulation time is considerably decreased (85). Deitrick (86) finds that immobilization in bed increased the tendency to faint on tilting subjects into the upright position. This decreased postural compensation with bed rest was not observed when subjects were kept in an oscillating bed.

The effects of positive and negative G on monkeys and dogs have been studied by Britton (87). The circulatory effects were considerably less in the monkey than in the cat or dog, the monkey having a physiological advantage of 0.5 to 1.0 G, according to the arterial pressure changes. Britton has restated Marey's Law as follows: "The heart rate is inversely and specifically related to the carotid artery blood pressure in the primate animal." [Compare Matthes & Ebeling (41).] Britton & French (88) have investigated numerous factors which modify the response to changes in G. Moderate haemorrhage reduces tolerance, as does anaesthesia and high environmental temperature. Tolerance is increased by struggling and a pelvic belt. Henry *et al.* (89) remarked that the mean cephalic arterial pressure may be as low as 20 to 30 mm. Hg, during positive G with no loss of consciousness. This they explain by the concurrent drop in the jugular venous pressure, so that the arterio-venous pressure difference may still amount to 60 mm. Hg. During negative acceleration, Shaw *et al.* (90) found that the venous pressure in the frontal vein varies linearly with acceleration, this increase in pressure being diminished by arterial occlusion on the thighs. It is considered that with negative G there may be a sustained increase in right atrial pressure of the order of 16 mm. Hg.

#### PERIPHERAL BLOOD FLOW

Regional differences in cutaneous blood flow are considerable. Hertzman & Randall (91) find that in a subject lying nude at a room temperature of 25 to 27°C. the blood flow in the finger pad is approximately 18 times the flow in the skin of the thigh. Pennes (92), from an analysis of temperatures in the forearm, has calculated the cutaneous flow. His figures are in fair agreement with those of Hertzman. Brecht & Pulfrich (93) have studied the varia-

tion in blood flow in the toes. They describe three types of fluctuation in flow which appear to be similar to those previously reported by Burch. The decrease in pulse volume and finger volume with a forced expiration is due to reflex vasoconstriction (94). Mead & Schoenfeld (95) have devised a technique for measuring blood flow in the terminal phalanx during different phases of the cardiac cycle. In the systolic phase the blood flow in the vasodilated phalanx is up to 200 cc. per 100 cc. tissue per min., falling to 130 cc. per 100 cc. per min. in diastole. Kerslake (96) has examined the effect of arterial occlusion at the wrist on forearm blood flow. The flow shows an initial increase, followed by a marked decline, with a steady flow after approximately 60 sec. occlusion. As it has been standard practice for many years to measure forearm flow with an arterial occlusion on the wrist, this finding has considerable importance in the interpretation of previous results. Landowne & Thompson (97) failed to obtain any reduction in reactive hyperaemia in man by the use of antihistamine drugs. However, this finding does not completely disprove the role of histamine in reactive hyperaemia as it is difficult completely to suppress the action of histamine in man. The effects of quantitative ischaemia have been studied by Guyton & Miller (98) with intermittent arterial occlusion. There is no appreciable diminution in flow with occlusion for 80 per cent of time, owing to reactive hyperaemia, but when the occlusion occupies 95 per cent of the cycle, there is severe ischaemic pain. Mercker & Schoedel (99) find that the effect of vasoconstrictor stimuli is greatly diminished during the period of increased blood flow following muscular activity. Blood flow is markedly diminished during maximal muscular contraction. This is compensated by the increased flow in regions of submaximal contraction and by reactive hyperaemia when contraction is over. Vessels supplying inactive motor units dilate during submaximal contraction of the rest of the muscle (100). Hill (101) has measured the pressure developed in the frog's gastrocnemius. During an isometric contraction, pressures as high as 300 mm. Hg were recorded. This finding lends added support to the view that the tension developed during maximal contraction is adequate to stop the arterial inflow.

There has been a considerable volume of work on the effects of temperature on the peripheral blood flow. Bader & Macht (102) find that heating the face is far more effective than heating the

chest or legs for increasing blood flow in the hands. Cooper & Kerslake (103) find that the increase in hand blood flow following heating of the legs may commence within 12 sec. and is not prevented by cutting off the circulation from the heated limbs and so must be due in part to direct stimulation of afferent nerve endings. Bader & Mead (104) have shown that the effects of local temperature on blood flow is markedly affected by body temperature. When the environmental temperature is kept at 32°C., the blood flow in the finger did not decrease on lowering the local temperature in the plethysmograph to 0°C. This effect may depend on the integrity of the vasomotor supply, as Perkins *et al.* (105) find that on keeping a dog in a warm atmosphere at 30°C., with the paws hanging out in an atmosphere between 0 and 5°C., there is sudden cooling in a sympathectomized paw at a time when the normal paw is still warm. When the whole animal is in a low environmental temperature, the normal limb cools gradually, whereas the sympathectomized limb will maintain a moderate temperature for some time, and then cool abruptly. These reactions in the sympathectomized limb exposed to cold are attributed to a sensitization of the denervated smooth muscle to cold, and possibly to a reduced formation of vasodilator metabolites.

Belding, Mead & Bader (106) measured skin temperature and digital blood flow in subjects who were moved from an environmental temperature of 32°C. to one of 13°C. The digital blood flow fell rapidly to 3 per cent of the original level, but the skin temperature lagged behind. On returning to the hot room, the skin temperature increased rapidly but the digital blood flow did not reach a steady level for over two hours. This is further evidence of the lack of correlation between blood flow and skin temperature. Bazett *et al.* (107, 108) have measured intra-arterial and intravenous temperatures in man. They have demonstrated the importance of the venae comites in heat exchange, and the marked cooling of arterial blood produced by the return of cold venous blood. It is suggested that there may be a reflex control of the venous circulation with increased flow in superficial veins when the limb is warm, and increased flow in the venae comites in the cold. Love (109) has measured foot blood flow in the summer and winter with the subject exposed to a hot and a cold environment. Aschoff (110) on theoretical ground has shown that the rate of blood flow must increase markedly at the periphery of the limbs. The vasomotor

reactions in normal skin, and in skin injured by frostbite, do not differ significantly according to Brecht & Pulfrich (111). Kramer & Schulze (112), in an excellent paper, describe the mechanism of vasodilatation in the cold. It appears to be due to an axon reflex as it can be abolished by infiltration with novocaine. Aschoff & Kaempffer (113) have examined the effect of vasoconstriction on heat exchange.

Pappenheimer, Eversole & Soto-Rivera (114) have studied the effects of varying the temperature of perfusing blood on the hind limb of the cat. As the temperature is lowered from 40°C. to 25°C. the blood flow diminishes; with further cooling the blood flow begins to increase and at a perfusion temperature of 5°C. to 10°C. the flow may be greater than at 40°C. The dilatation with cold blood is in the muscle vessels and can be abolished by sodium cyanide; the rate of blood flow then decreases with temperature as viscosity increases. According to Howarth, McMichael & Sharpey-Schafer (115), the low blood pressure in diabetic coma is due to a peripheral vasodilatation.

Kety *et al.* (121) have observed cerebral vasodilatation in diabetic coma. Cohen *et al.* (116) have examined the effects of arteriovenous aneurysms on the circulation. The blood flow in the region distal to the aneurysm is at first reduced and slowly increases over a period of many years. On closure of the aneurysm, the blood flow in unaffected limbs is increased owing to a reflex vasodilatation.

#### CIRCULATION IN SPECIAL REGIONS

*Cerebral blood flow.*—The physiology of the cerebral circulation has been comprehensively reviewed by Bouckaert & Jourdan (117). Kety and his colleagues have measured the cerebral blood flow in man under a variety of conditions, using the nitrous oxide technique (118 to 124). Kety & Schmidt (118) have examined the theory of the method and answered certain criticisms. There was no essential difference using right or left internal jugular blood in the calculated flood flow. Contamination with extracerebral blood is estimated to be approximately 2.6 per cent. Good agreement was found between measurements made with the bubble flow meter and the nitrous oxide technique in monkeys. Kety & Schmidt (119) find that increased tension of carbon dioxide increases cerebral blood flow and reduces cerebrovascular resistance, whereas an increased oxygen tension caused a slight but definite cerebral vaso-

constriction. There is a marked cerebral vasodilatation with reduced oxygen tension.

Increased intracranial pressure does not consistently reduce the cerebral blood flow until the pressure reaches 450 mm. water. further increase in pressure then results in progressive reduction; When the cerebral blood flow fell below 400 cc. per 100 gm. brain per min., all patients became comatose (120).

In diabetic acidosis, with little evidence of circulatory failure, the cerebral blood flow was reduced below normal, but in diabetic coma with severe circulatory collapse, the cerebral blood flow was increased, but the oxygen consumption then was only half of the normal value. There was no relationship in these cases between cerebral oxygen consumption and cerebral blood flow, but there was a significant correlation between cerebral blood flow and arterial pH (121). Cerebral blood flow is normal in hypertension but cerebrovascular resistance is increased, so the cerebral vessels are also involved in the generalized increase in vascular tone (122). When arterial pressure was reduced in hypertension by differential spinal anaesthesia, cerebral blood flow fell, but there was no reduction in cerebrovascular resistance (123). Shenkin *et al.* (124) find that passive tilting into the head-up position reduces the cerebrovascular resistance, but cerebral blood flow is unchanged. In patients with cerebral tumors, tilting increased resistance and reduced cerebral blood flow. In the head-down position, in spite of an increased mean blood pressure, the cerebral blood flow diminished in normal subjects, but in patients with cerebral tumors the cerebrovascular resistance and blood flow were unaltered. McCall (125) finds that in normal pregnancy and in toxæmia of pregnancy, cerebral blood flow is unchanged.

Sjöstrand (126) has shown that inhalation of carbon monoxide dilates the small vessels in the pia mater. Histamine dilates the cerebral arteries, although the external carotid constricts, according to Poupa (127). Noell & Schneider (128) have measured the cerebral blood flow in the anaesthetized dog and found a constant value of 40 cc. per 100 gm. brain per min. with an oxygen consumption of 2.8 cc. Both these figures are lower than those reported by Kety in man. Harmel *et al.* (129) report that stellate block in man does not increase cerebral blood flow. According to Guyton (130) the rise of arterial pressure produced by acute cerebral ischaemia is not completely abolished by section of the vagi and denervation

of the carotid sinus, and therefore there is a direct effect on the vasomotor centres. The blood flow in the circle of Willis has been examined by McDonald & Potter (131). The internal carotid and vertebral blood flows normally do not mix in the anastomotic vessels, but each supply their own separate territory.

*Blood flow in the umbilical vessels.*—Cooper, Greenfield & Huggett (132) using a plethysmograph (16) have measured the rate of blood flow in the umbilical vessels in the sheep; their technique is described by Cooper & Greenfield (133). The blood flow increases with the age of the fetus, but blood flow per unit body weight declines with age. Their figures, which were obtained with the fetus in an excellent condition and with a minimum of disturbance, are slightly higher than those previously reported by Barcroft (134).

*Splanchnic circulation.*—Richins & Brizzee (135) find that the duodenal arterioles in the rat constrict and dilate in response to cooling or heating of the abdominal wall. Acute intestinal distension causes a sharp fall in blood pressure, according to two different groups of workers (136, 137).

*Hepatic circulation.*—Myers & Holland (138) and Myers & Hickam (139) have studied hepatic blood flow. In cardiac failure, with a low cardiac output, the hepatic blood flow is proportionately decreased, whereas in anaemia with a high cardiac output, the hepatic blood flow is proportionately increased. Ashworth & Haist (140) measured hepatic blood flow before and after anastomosis of the portal vein to the inferior vena cava. Before the anastomosis, restriction of portal vein blood flow caused a marked fall of arterial pressure, but after anastomosis, constriction of the portal vein did not reduce arterial pressure or blood flow to the liver. Cohn, Levine & Kolinsky (141) have criticized the use of bromsulphalein for measuring hepatic blood flow, on the grounds that even at high plasma levels of the dye the tissues do not become saturated.

*Renal circulation.*—Chapman and his colleagues (142, 143) have shown that the decline in renal plasma flow with exercise is progressive for the first hour and then levels off, the extent of the decline being proportional to the severity of the exercise. The effect of raising the pressure in the renal vein on renal blood flow has been examined by Selkurt, Hall & Spencer (144) who found an average decline of only 15 per cent in blood flow when venous pressure was

raised from 7.5 mm. Hg. to 22.5 mm. Hg; this fall can be explained by the decreased arteriovenous pressure gradient. Blake *et al.* (145) report similar results, i.e., with renal vein pressures raised to 350 mm. saline there was no significant decline in renal plasma flow, but with further increase in pressure, flow decreased. However, as venous pressure rose, urine volume diminished as did the total sodium excretion. The authors suggest that a significant factor in cardiac edema is the retention of water and sodium due to increased pressure in the renal vein. Bull (146) considers that postural proteinuria, which can be easily induced in young subjects, is due to a rise of pressure in the renal vein, owing to compression of the inferior vena cava by the posterior surface of the liver. Renal vessels are constricted as a result of inhalation of 10 per cent carbon dioxide (147). Hypoxia does not affect the renal circulation (148). Additional studies on renal blood flow are reviewed in the chapter on the kidney by Trueta in this volume.

*Pulmonary circulation.*—Nisell (149) reports that oxygen and carbon dioxide exert a direct action on the pulmonary vessels. Donnet *et al.* (150, 151, 152) provide further evidence that there are pressoreceptors in the pulmonary circulation. Pulmonary capillary pressure has been measured by Hellems *et al.* (153), using the end pressures recorded with catheters passed up the pulmonary artery and vein until they block. The average mean pressure was 8.3 mm. Hg.

#### CAPILLARIES

Chambers (154) has reviewed his studies of the capillary circulation. Nicoll & Webb (155) have made direct observations of the small blood vessels in the bat's wing; there is a rhythmical relaxation and contraction of the entire terminal arteriole with corresponding changes of flow in the capillaries supplied. Haley & Harris (156) report that antihistamine substances constrict the precapillary sphincters which are relaxed by histamine. The velocity of blood flow in capillaries has been studied by Laszt (157) by means of motion pictures; the average velocity was 1.2 mm. per sec. Morel & Marois (158) have measured capillary permeability in the rabbit with radioactive sodium. Silver & Reed (159, 160) have used the rate of disappearance of T 1824 as a measure of capillary permeability. Histamine markedly increased the rate of disappearance; increased plasma cholesterol had no effect on permeability, whereas large doses of vitamin D significantly dimin-

ished permeability. Elster, Freeman & Dorfman (161) gave hyaluronidase and T 1824 intravenously to rats. There was a rapid diffusion of the dye into the tissues as compared with controls and there was marked edema corresponding to the distribution of the dye. Sturm (162) has studied the mechanism of permeability, and from experiments on models concludes that filtration of fluid from and absorption into capillaries depends on the shape of the vessels concerned, fluid leaving the capillaries where they narrow, and re-entering the blood stream as the vessels become wider. He does not consider that osmosis plays an important part. Lazarus (163) discusses critically various capillary tests in scurvy.

#### VENOUS CIRCULATION

Pollack and his colleagues (164, 165) have measured venous pressure at the ankle, using a strain gauge manometer (22). In normal subjects and in patients with varicose veins the venous pressure is similar in the supine and standing positions, but when the subjects walk on a tread mill there is a striking difference. In normal subjects the venous pressure falls rapidly and remains at a low level. The fall of venous pressure in subjects with varicose veins is minimal and shows marked fluctuations with each step. These experiments demonstrate very clearly the importance of the valves in the venous circulation. Hickam, McCullough & Reeves (166) report similar findings. They also discuss the mode of drainage from the superficial to the deep veins and the functions of the valves. Tichy & Shaw (167) were able to double the blood flow in the femoral vein of the dog by faradic stimulation of the leg muscles. Volwiler *et al.* (168) have recorded the pressure in the inferior vena cava and portal vein in the unanaesthetized dog. Progressive constriction of the thoracic vena cava, producing ascites and hepatic congestion, only increased venous pressure slightly. Levy & Burch (169) found that the pressures in a foot vein and veins of the abdominal wall are slightly increased in hepatic cirrhosis with ascites.

#### CIRCULATION TIME

Corboz (170, 171) measured arterial blood velocity in man by injecting methylene blue or Geigy blue into the femoral artery and timing the arrival of the dye at the toe with a photoelectric

plethysmograph. In the horizontal position the velocity averages 7 cm. per sec., but the axial speed appears to be from 15 to 28 cm. per sec. Freis, Stanton & Emerson (172) have injected tagged red cells and dyed plasma intra-arterially, and found that the mean velocity of the cell mass is significantly greater than the plasma. T 1824 has been used by Miller (173) to measure the arm to ear circulation time, with an ear photometer, giving an average time of 14.2 sec. Circulation time can be measured accurately and objectively by injecting acetylcholine, the end point being the onset of cardiac slowing recorded electrocardiographically. However, Schlichter *et al.* (174) report that it is not entirely a safe method.

Stanton, Freis & Wilkins (175) have measured the velocity of flow in leg veins, timing the progress of diodrast with a fluoroscope and serial x-rays. The first appearance of diodrast observed in the upper third of the thigh was 22 sec. after injection into an ankle vein and this time was reduced to 11 sec. on application of a pressure of 20 mm. Hg. over the whole leg, flow being equally accelerated in both superficial and deep veins. Wright, Osborn & Edmonds (176), using radioactive sodium and a Geiger counter found that the average time from the ankle to the thigh was 18 sec., and this time was not altered by immersion of the leg in water at 45°C. Gillespie & Reynolds (177) have devised a technique for measuring circulation time in the uterus by following the rate of clearance of diodrast injected with a hypodermic through the abdominal wall into the uterus. Ogden, Clouse & Murray (178) have used the time interval between intradermal injection of histamine and the appearance of the flare as an index of the rate of the local cutaneous circulation.

#### BLOOD VOLUME

A simplified technique for measuring blood volume with radioactive corpuscles has been described by Zerah (179). Allen & Orahovats (180) have refined a procedure for measuring quantities of T 1824 as small as 0.5 $\mu$ g. Sjöstrand (181) describes a method for determination of the total haemoglobin content of the body with carbon monoxide. The electric resistance of blood has been used to measure cell volume by Rosenthal & Tobias (182); this method gave values which were 7.7 per cent lower than the haematocrit. Mendlowitz (183) describes a simple technique for measuring blood volume by determining the haematocrit before and

after the intravenous injection of 600 cc. plasma. There are some obvious limitations with this technique. It is widely recognized that a major source of error in the measurement of blood volume is due to the trapping of plasma with red cells in the determination of the haematocrit. McLain & Ruhe (184) have investigated a number of methods for measuring the proportion of red cells to plasma. They conclude that no method is as yet sufficiently accurate to be preferred. Apart from the difficulties of measuring the haematocrit there is the problem whether the haematocrit from peripheral vessels is representative of the whole blood volume. Ederstrom (185) has shown that red cell counts in blood samples drawn from different peripheral vessels and direct from the heart or large vessels do not differ significantly. Barnes, Loutit & Reeve (186, 187) have compared blood volume measurements made with T 1824 and marked red cells. Red cell volume estimated with T 1824 and haematocrit gives results 15 per cent higher than with the tagged cell techniques, although a correction was made for the haematocrit containing 5 per cent plasma. The various possible errors of the dye method are considered in detail, particularly the factors affecting the loss of dye from the circulation. However, the initial mixing phase of dye and marked red cells which are unlikely to escape from the circulation appears to be similar. It is considered that the chief source of the overestimate with T 1824 is due to an unequal distribution of plasma and red cells in the circulating blood volume. A comparison of the dye method and tagged cell method, using  $P^{32}$  made by Kelly, Simonson & Elman (188), showed fair agreement; the volume estimated by T 1824 being slightly higher. Another comparison has been made by Kreiger *et al.* (189), who measured plasma volume with T 1824 and injection of protein tagged with radioactive iodine. Subsequently, the red cell volume was measured using  $P^{32}$ . They also found a larger blood volume with the dye method than with  $P^{32}$ , but the iodine method gave results slightly smaller than the tagged red cells. Mayerson *et al.* (190), using a technique described by Nieset *et al.* (191), obtained good agreement between T1824 and  $P^{32}$  values. They employed a correction of 8.5 per cent for plasma trapped in haematocrit as compared with 5 per cent used by Barnes *et al.* (186). Reeve & Veall (192), also using  $P^{32}$ , found considerably higher values with T 1824; the discrepancy between these two groups is partly accounted for by the different correction

factor employed for the volume of plasma trapped in the haematocrit. Hamilton *et al.* (193) found that the red cell count varies with dye plasma volume closely, and describe a simple way of following changes in blood volume, using the red cell count. Nizet (194) has used red cells labelled with phenylhydrazine. In a preliminary note, McLain, Ruhe & Kruse (195), have reported blood volumes in the rabbit measured by T 1824, and by complete bleeding out and washing through the circulatory system, the latter giving markedly lower values. Courtice & Gunton (196) draw attention to the varied results reported in the literature using T 1824. They have used the carbon monoxide method and obtained good agreement with T 1824. Exercise did not significantly lower blood volume, whereas Cullumbine and Koch (197), using the changes in the haematocrit and plasma protein, conclude that with exercise there is considerable decrease in plasma volume which takes up to an hour to return to normal. Courtice & Gunton (198, 199) have shown that anaesthesia affects blood volume. The uptake of carbon monoxide is slower under pentobarbital anaesthesia and in dogs the plasma volume increases and total red cell volume falls. But the effects of anaesthesia on blood volume are revealed more clearly by the response to haemorrhage; nembutal notably decreases haemodilution after blood loss, particularly in the dog. Rossiter (200) has shown that the rate of disappearance of T 1824 from the circulation increases as the plasma albumin level falls. This may account for some of the anomalous results of blood volume determination in disease. Nylin & Hedlund (201) discuss the technique of using cells labelled with  $P^{32}$ . They show that the cardiac output may be calculated from the dilution curve. Cohn & Shock (202) did not find any significant change in the ratio of blood volume and body weight with age. Wang & Hegsted (203), measuring blood volume in rats, found it was proportional to body weight only up to puberty, thereafter body weight increased more rapidly than plasma volume. Braun-Menendez & Covian (204) have also studied blood volume and thiocyanate space in rats with similar results. Parson *et al.* (205) were unable to detect any difference in red cell or plasma volume after epinephrine in man. Speakman *et al.* (206) find that physical performance correlates well with blood volume levels, and the improvement observed during acclimatization to heat may be due to the increased blood volume found at that time. Total haemoglobin does not appear to

increase consistently during hot weather although there is a significant increase in reticulocytes (207).

Pressure breathing reduces blood volume significantly, according to Henry *et al.* (208). A pressure jacket does not decrease the loss, but there is a reduction with counter pressure on the legs. Altschule & Cline (209) find that there is a decrease in plasma volume after electric shock therapy. Pickering & Dow (210) have measured the mixing time when brilliant vital red is injected, by comparing serial samples of arterial and venous blood. It is normally complete in four minutes, but after haemorrhage the results are highly variable.

#### HAEMORRHAGE AND SHOCK

Glasser & Page (211) have modified the technique of Wiggers & Werle for producing a standardized degree of haemorrhagic shock in dogs, by bleeding from an artery into a reservoir kept at a desired pressure. In this way the arterial pressure can be kept constant at any desired level, and during the period of hypotension blood will pass into or out of the reservoir. At the end of the hypotensive period, blood is retransfused intra-arterially which is more effective than the intravenous route as there is retrograde flow up the aorta to the coronaries and the vessels of the brain and spinal cord. The great variation in the ability of animals to withstand severe hypotension is stressed. Remington *et al.* (212) have shown also that the compensatory vasoconstriction after haemorrhage may be detrimental if prolonged. Using dibenamine to prevent vasoconstriction they found that nine out of 10 dogs survived a degree of haemorrhage which killed 13 out of 14 controls. Dibenamine also protected animals against the effects of trauma. There does not appear to be a significant vasoconstriction in muscle vessels in man following moderate haemorrhage (213).

Allison *et al.* (214) have compared the effects of whole blood and plasma transfusions in haemorrhagic shock, the former being significantly more effective. Nastuk & Beatty (215, 216) have studied various biochemical changes in haemorrhagic shock and find that the extent and duration of the plasma bicarbonate depression correlates with the degree of shock. They have calculated a stress index based on these changes. The effects of whole blood transfusion were compared with whole blood combined with bicarbonate and whole blood combined with glucose. These were

given to animals with comparable stress indices, but there were no significant differences in the results. Beatty (217) has studied glucose metabolism after haemorrhage. Kline (218) has followed blood amino nitrogen levels in normal and diabetic animals following haemorrhage. Mazur & Shorr (219) have now identified VDM as ferritin; it has also been shown that ferritin is an antidiuretic (220). Corcoran *et al.* (221) were unable to find any consistent effect of ferritin on the arterial pressure or epinephrine response in the rat, although very large doses were used. The role of the liver and kidney in haemorrhagic hypotension has been stressed by Zweifach & Shorr, as summarized by Ogden in the previous volume of the *Annual Review of Physiology*. These views have been criticized by Reinhard, Glasser & Page (222) who have studied the effects of haemorrhage in nephrectomized and hepatectomized animals. Their results did not demonstrate a critical function of liver or kidneys in the vascular response to haemorrhage. Grandpierre *et al.* (223) find that haemorrhage in dogs reduces the pressor effect of epinephrine even when arterial pressure is maintained. Post & Spealman (207) find that after a venesection of 500 cc. complete regeneration of the lost haemoglobin may take up to four weeks. A haemorrhage of this order reduces physical performance significantly (206). Rau (224) gives evidence to suggest that blood hypertensinogen often is increased after haemorrhage.

#### ANOXIA AND ASPHYXIA

Feldman, Rodbard & Katz (225) have studied the distribution of circulating blood in acute hypoxemia. Before the arterial pressure falls there is a marked increase in the blood flow in the superior vena cava with a concomitant decrease in the inferior vena cava, so a higher proportion of the cardiac output is going to the head. The initial rise of blood pressure in acute anoxia is not due to epinephrine which is, however, responsible for the posthypoxaemic rise, according to Van Loo, Surtshin & Katz (226). Marsh & van Liere (227), however, find that epinephrine-blocking agents abolish the rise of blood pressure induced by anoxia. Göpfert (228) has studied the effects of asphyxia and anoxia in cross-circulation experiments. The vasomotor centres in the spinal cord appear to be insensitive to carbon dioxide. Binet, Burstein & Lemaire (229, 230) find that the peripheral vasomotor reactions during hypoxia are variable but there is marked vasodilatation with reoxygena-

tion which is abolished by denervation. Malmejac, Chardon & Gross (231, 232, 233) have shown that the vasomotor centres survive prolonged hypoxia longer than the respiratory centre. During the stage of low arterial pressure there is a peripheral vasoconstriction mediated by the vasomotor centre. The spleen in the dog contracts only when arterial oxygen saturation falls below 40 per cent, according to Kramer & Luft (234). Bonsdorff & Jalavisto (235) suggest that the erythrocytosis of anoxia is due to a humoral mechanism. Grandjean (236) reports that at high altitudes there is a diminution in hand volume, probably due to tissue dehydration. This may be related to the decreased capillary permeability at high altitudes. Frank & Wezler (237, 238) have examined the circulation in anoxia at different environmental temperatures. Cutaneous vasoconstriction at low temperatures is less efficient during anoxia, and at high environmental temperatures circulatory failure occurs more commonly with anoxia.

#### PHARMACOLOGY

There have been a number of papers concerned with norepinephrine and there is now considerable evidence to show that this substance is produced in the suprarenal glands and elsewhere in the body. Von Euler (239, 240) has identified the sympathomimetic substance in extracts of splenic nerve as norepinephrine. These findings are confirmed by Peart (241). Holton (242) finds more norepinephrine than epinephrine in adrenal tumors. Similar findings are reported by Goldenberg *et al.* (243), who also obtained norepinephrine in extracts of normal adrenal glands. Tullar (244) and Auerbach & Angell (245) report that the official U.S.P. epinephrine contains from 10.5 to 18.0 per cent norepinephrine. The effects of epinephrine and norepinephrine have been compared in the cat by Folkow *et al.* (246). Norepinephrine constricts muscle as well as splanchnic vessels, and these effects were abolished but not reversed by dibenamine. Goldenberg *et al.* (247) have shown that norepinephrine raises the total peripheral resistance in man, whereas it is lowered by epinephrine; these effects are increased in hypertensives. Barcroft & Konzett (248, 249) find that norepinephrine constricts muscle vessels in man, and similar findings are reported by Duncanson, Stewart & Edholm (250). Traces of norepinephrine restore the action of epinephrine in adrenalectomized dogs (251). The effects of hepatic nerve stimulation and

injection of norepinephrine are similar according to West (252). He has also found that after doses of ergotoxine which reverse the action of epinephrine, small doses of norepinephrine are pressor but very large doses are depressor (253). Graham (254, 255) has confirmed that norepinephrine has a more powerful pressor effect in the spinal cat than does epinephrine, and the pressor effects of both are inhibited by atropine.

There are many papers dealing with the action of adrenolytic and ganglion-blocking drugs. The dihydrogenated derivatives of the ergot alkaloids, dihydroergocorine (DHO) and dihydroergocryptine (DHE), introduced by Rothlin (256), are sympatholytic and adrenolytic (257). DHO markedly increases limb blood flow (259). It reduces the arterial pressure of hypertensive but not of normal individuals (258, 259).

Tetraethylammonium (TEA) is extensively used to block autonomic ganglia. Moe *et al.* (260), using a continuous infusion of TEA in dogs, abolished the pressor effect of carotid artery occlusion and effect of stimulation of the depressor nerve. The pressor effect of epinephrine was increased with reduced femoral artery blood flow, whereas in the absence of TEA, epinephrine increased femoral artery flow, suggesting that the dilator effect is reflex in origin. TEA has little effect on either arterial or venous pressures in normal subjects, according to Relman & Epstein (261), but in congestive heart failure there is a considerable fall in both. The effect of body warming, TEA and Priscol on the peripheral circulation has been compared by Green & Ogle (262). Body warming raised finger temperature higher than Priscol, which was in turn more effective than TEA, whereas in the toes Priscol had a greater effect than TEA on body warming. TEA has a less effective and more unreliable vasodilator effect than peripheral nerve block according to Pearl (263, 264). Some of these effects of TEA may be explained by a preliminary report from Page *et al.* (265) suggesting that TEA may liberate a norepinephrine-like substance. Morrison & Farrar (266) blocked the release of epinephrine from the adrenal medulla with TEA. Hoobler *et al.* (267) measured the effect of various procedures on the blood flow through the feet; a more reliable procedure than measuring changes in skin temperature. TEA produced a greater increase than body warming, but paravertebral block or caudal anaesthesia produced much larger flows. Dibenamine acts by combining with the epinephrine

receptors, as shown by Seed & McKay (268). Epinephrine increases blood flow in muscle vessels but reduces local metabolism according to Gollwitzer-Meier (269). Bülbring & Burn (270) report that acetylcholine can have a constrictor effect as well as a dilator effect on blood vessels. Wakim and his colleagues (271) have investigated the effects of histamine, given intravenously for 20 min., on the peripheral blood flow. Cutaneous vasodilatation appeared first on the face and gradually spread downwards, involving the lower extremities only at the end of the infusion. There was a gradual increase in limb flow, greater in the arms than legs.

In the hind limb preparation, Binet & Burstein (272) obtained arteriolar dilatation with intra-arterial injections of histamine. Weber & Steggerda (273) have correlated the fall of arterial pressure following x-ray irradiation with the plasma histamine level.

Macht (274) has investigated the effects of amino acids on peripheral blood flow; glycine caused a substantial increase in hand flow, other amino acids were relatively ineffective. Holmstedt & Wretling (275) injected intravenously a casein digest containing 67 per cent free amino acids to cats and rats; the arterial pressure rose and Traube-Hering waves were suppressed.

Carbon monoxide causes intense peripheral vasoconstriction but in the denervated limb there is dilatation, according to Binet & Burstein (276).

#### HYPERTENSION

The relationship of the adrenal gland to hypertension has been comprehensively reviewed by Sapeika (277). Smirk (278) and Page (279) have reviewed the pathogenesis of hypertension, Boyton & Todd (40) have shown that a family history of hypertension is associated with a slightly higher than average systolic arterial pressure. Kilpatrick (280) has discussed the variations in casual and basal arterial pressure both in normals and hypertensives.

Green, Coleman & McCabe (281) found that the pressor effect of small doses of desoxycorticosterone acetate (DOCA) was potentiated by the substitution of saline for drinking water, but there was no potentiation of large doses. Green (282) observed that the hypertensive action of small doses was reduced by adrenalectomy, but this had no effect with large doses. He suggests that the rise

in arterial pressure may be a compensatory mechanism to overcome the disturbance in fluid and electrolyte balance. Skahen & Green (283) have shown that DOCA increases the output of anti-diuretic factor, but this is not related to the degree of hypertension. Friedman *et al.* (284), using large doses of DOCA, found no significant difference between control and adrenalectomized rats. Freidman & Freidman (285) increased the hypertensive effect by nephrectomy. Summers (286) was unable to raise the arterial pressure with large doses of DOCA given intramuscularly to dogs on a high sodium chloride intake. However, Davis *et al.* (287) obtained a sustained pressor effect in both normal and renal hypertensive dogs with subcutaneous injections of DOCA; intravenous injections of DOCA had no effect. In man, Goldman & Schroeder (288) raised the diastolic pressure in hypertensive patients with intravenous DOCA, although there was no action in normal subjects.

#### THE ROLE OF THE KIDNEY IN HYPERTENSION

Although a purely renal concept of hypertension is no longer generally accepted, the role of the kidney is clearly of importance. However, Black *et al.* (289) consider that the hypertension in nephritis is not due to the renin mechanism. An important paper by Grollman, Muirhead & Vanatta (290) describes the effects of bilateral nephrectomy in dogs. Using an artificial kidney, survival was maintained for five to seventeen days, and in all animals after the third day there was a progressive rise in arterial pressure, with pathological changes characteristic of hypertension. These changes are clearly not due to any positive renal action. However the effects of renin may not be entirely excluded as de la Barreda *et al.* (291) report that a renin-like substance can be produced from arterial walls. Braun-Menendez & Covian (292) also found hypertension developing in some 30 per cent of nephrectomized rats. Pressor substances were detected in the blood of patients with hypertension and renal disease by Schroeder, Goldman & Olsen (293), although these pressor substances were not found in the majority of neuro-genic hypertensives. Goldman *et al.* (294) found that transfusion of blood from hypertensive subjects caused a rise in diastolic blood pressure, which was not found with normal blood. Gollan, Richardson & Goldblatt (295) have succeeded in demonstrating hypertensin in the blood of dogs with experimental renal hypertension;

none was found in control animals. Flasher (296) found that the hypertension, developing as a result of unilateral renal ischaemia, persisted for several weeks after removal of the ischaemic kidney. Ogden *et al.* (297) report that periadrenal tissue ligation increases systolic pressure. But with the same procedure, Canham & Wakerlin (298) could only produce an effect in one out of six dogs. Auditory stress prolonged for eight to eleven months produces hypertension in rats. Although no significant change could be detected in the adrenals, adrenalectomy lowers the arterial pressure, which does not rise even if auditory stress is continued (299, 300).

#### SYMPATHECTOMY AND AUTONOMIC BLOCKADE

There are several reports reviewing the effects of sympathectomy (301, 302, 303). Wilkins, Culbertson & Halperin (304) found that hepatic blood flow is greatly increased two weeks after sympathectomy, then gradually declines. Splanchnic vasoconstriction in the upright position is reduced. Wolff *et al.* (305) observed rises in arterial pressure in response to stress even after sympathectomy.

The effective renal blood flow is reduced in hypertension (306) but the ratio of renal to nonrenal vascular resistance falls after sympathectomy (307). Taylor *et al.* (308) found a poor correlation between the falls of arterial pressure produced by spinal anaesthesia and the effects of sympathectomy. Corcoran, Taylor & Page (309) consider that the haemodynamic effects of spinal anaesthesia and sympathectomy differ, and in particular they find that renal blood flow is increased by anaesthesia but not by sympathectomy. Dibenamine produced orthostatic hypotension in hypertensive patients (310). The arterial pressure of renal hypertensive rats was lowered by dibenamine (311). Taylor & Page (312) have found that TEA produces highly variable effects on the arterial pressure of renal hypertensive dogs. Stead *et al.* (313) tested the effect of a low salt diet on the response to TEA. In those subjects with a marked fall of arterial pressure after TEA, salt deprivation produced a lowering of resting arterial pressure, but this was not found in subjects who did not respond to TEA. These findings imply that a low salt diet only is effective when hypertension is primarily neurogenic. Soloff *et al.* (314) found a poor correlation between the effects of TEA and spinal anaesthesia compared with sympathectomy. Second and TEA have very similar effects on diastolic arterial pressure in hypertension, according to Frew &

Rosenheim (315). Part of the differences reported in the literature concerning the effects of TEA is probably due to the fact that the drug is not consistently used with the patient in the basal state.

## LITERATURE CITED

1. OGDEN, E., *Bull. N. Y. Acad. Med.*, **24**, 561-85 (1948)
2. MARVIN, H. M., *Bull. N. Y. Acad. Med.*, **24**, 720-42 (1948)
3. PETERSON, L. H., DRIPPS, R. D., AND RISMAN, G. C., *Am. Heart J.*, **37**, 771-82 (1949)
4. EATHER, K. F., PETERSON, L. H., AND DRIPPS, R. D., *Anesthesiology*, **10**, 125-32 (1949)
5. TOMPKINS, H. E., *Am. Heart J.*, **37**, 783-89 (1949)
6. LAMBERT, E. H., AND JONES, R. E., *Proc. Staff Meetings Mayo Clinic*, **23**, 487-93 (1948)
7. MARSH, D. F., *Science*, **108**, 393 (1948)
8. MARSH, D. F., *J. Lab. Clin. Med.*, **34**, 143-45 (1949)
9. FRIEDMAN, M., AND FREED, S. C., *Proc. Soc. Exptl. Biol. Med.*, **70**, 670-72 (1949)
10. SEGERS, M., AND HENDRICKY, J., *Arch. intern. physiol.*, **56**, 196-97 (1948)
11. SCHLAPP, W., AND WALKER, A. G., *J. Physiol. (London)*, **108**, 458-66 (1949)
12. LOUCKS, W. W., KOSTASHUK, S. S., AND BURTON, A. C., *Can. J. Research [F]*, **26**, 447-56 (1948)
13. CURTIS, H. J., AND NICKERSON, J. L., *Proc. Soc. Exptl. Biol. Med.*, **70**, 383-84 (1949)
14. GOODYER, A. V. N., *J. Clin. Invest.*, **27**, 536 (1948)
15. KERSLAKE, D. M., *J. Physiol. (London)*, **108**, 398-404 (1949)
16. GREENFIELD, A. D. M., *J. Physiol. (London)*, **108**, 157-59 (1949)
17. ROBERTSON, C. W., AND SMITHWICK, R. H., *J. Lab. Clin. Med.*, **34**, 438 (1949)
18. PROBST, J. M., AND FLEISCH, A., *Helv. Physiol. et Pharmacol. Acta*, **7**, C17-18 (1949)
19. CERLETTI, A., AND ROTHLIN, E., *Helv. Physiol. et Pharmacol. Acta*, **6**, 92-113 (1948)
20. MOE, G. K., *Science*, **109**, 381 (1949)
21. SELKURT, E. E., *J. Lab. Clin. Med.*, **34**, 146-50 (1949)
22. POLLACK, A. A., AND WOOD, E. H., *Am. Heart J.*, **36**, 899-905 (1948)
23. KAY, C. F., WOODS, J. W., JR., ZINSSER, H., AND BENJAMIN, J. M., *J. Clin. Invest.*, **28**, 228-37 (1949)
24. SCARBOROUGH, H., ELKIN, M., BLISS, H. A., PARK, H. W., AND LANDIS, E. M., *Am. J. Physiol.*, **155**, 467 (1948)
25. CRESSON, S. L., AND GLENN, W. W. L., *J. Lab. Clin. Med.*, **33**, 1597-1602 (1948)
26. McDOWALL, R. J. S., *J. Physiol. (London)*, **108**, 2P-3P (1949)
27. LAMFORT, H., *Federation Proc.*, **8**, 90-91 (1949)
28. BURTON, A. C., *Am. J. Physiol.*, **155**, 430 (1948)
29. WILLIAMS, A. H., AND SCHROEDER, H. A., *Am. J. Physiol.*, **155**, 133-40 (1948)

30. VAN HARREVELD, A., FEIGEN, G. A., AND LERMAN, L. S., *Am. J. Physiol.*, **157**, 168-76 (1949)
31. MÜLLER, A., *Helv. Physiol. et Pharmacol. Acta*, **6**, 181-95 (1948)
32. TIMM, C., *Arch. ges. Physiol. (Pflügers)*, **249**, 261-79 (1947)
33. MENDLOWITZ, M., *J. Clin. Invest.*, **27**, 565-71 (1948)
34. KEAN, B. H., AND HAMMILL, J. F., *Arch. Internal Med.*, **83**, 355-62 (1949)
35. GOVER, M., *U. S. Pub. Health Service, Pub. Health Repts.*, **63**, 1083-1101 (1948)
36. NIEUWMEIJER, A. H., AND BRANDSMA, K., *Arch. Internal Med.*, **83**, 429-53 (1949)
37. BERRY, W. T. C., BEVERIDGE, J. B., BRANSBY, E. R., CHALMERS, A. K., NEEDHAM, B. M., MAGEE, H. E., TOWNSEND, H. S., AND DAUBNEY, C. G., *Brit. Med. J.*, **1**, 300-4 (1949)
38. THOMSON, A. E., AND DOUPE, J., *Can. J. Research [E]*, **27**, 72-80 (1949)
39. MORSE, M., SCHLUTZ, F. W., AND CASSELS, D. E., *J. Applied Physiol.*, **1**, 683-709 (1949)
40. BOYNTON, R. E., AND TODD, R. L., *Am. J. Med. Sci.*, **216**, 398-402 (1948)
41. MATTHES, K., AND EBELING, J., *Arch. ges. Physiol. (Pflügers)*, **250**, 747-68 (1948)
42. VAN LIERE, E. J., STICKNEY, J. C., AND MARSH, D. F., *Science*, **109**, 489 (1949)
43. PETERSON, L. H., SCHNABEL, T. G., FITZPATRICK, H., AND BAZETT, H. C., *Am. J. Physiol.*, **155**, 460 (1948)
44. HERXHEIMER, H., *J. Applied Physiol.*, **1**, 279 (1949)
45. CHAPMAN, W. P., LIVINGSTON, R. B., AND LIVINGSTON, K. E., *J. Clin. Invest.*, **27**, 529 (1948)
46. JOHNSON, A. C., HOFF, E. C., GRAY, E. H., AND SHOLES, D. M., *Am. J. Physiol.*, **155**, 446 (1948)
47. HOFF, E. C., JOHNSON, A. C., SHOLES, D. M., AND GRAY, E. H., *Am. J. Physiol.*, **155**, 443-44 (1948)
48. HOFF, E. C., KELL, J. F., JR., HASTINGS, N., GRAY, E. H., AND SHOLES, D. M., *Federation Proc.*, **8**, 76 (1949)
49. HEYMANS, C., AND PANNIER, R., *Arch. intern. pharmacodynamie*, **77**, 56-57 (1948)
50. LEUSEN, I., *Arch. intern. pharmacodynamie*, **77**, 48-49 (1948)
51. LEUSEN, I., *Arch. intern. pharmacodynamie*, **77**, 50-51 (1948)
52. NEIL, E., REDWOOD, C. R. M., AND SCHWEITZER, A., *J. Physiol. (London)*, **108**, 8P (1949)
53. DOUGLAS, W. W., INNES, I. R., AND KOSTERLITZ, H. W., *J. Physiol. (London)*, **108**, 17P (1949)
54. DOUGLAS, W. W., INNES, I. R., AND KOSTERLITZ, H. W., *J. Physiol. (London)*, **107**, 48P (1948)
55. SIGLER, L. H., *Ann. Internal Med.*, **29**, 687-97 (1948)
56. ROSENBERG, H., *J. Physiol. (London)*, **107**, 29P (1948)
57. JARISCH, A., AND ZOTTERMAN, Y., *Acta Physiol. Scand.*, **16**, 31-51 (1948)
58. CHATONNET, J., AND VIAL, J., *Compt. rend. soc. biol.*, **142**, 97 (1948)
59. SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L., *Am. J. Physiol.*, **154**, 297-327 (1948)

60. AUTIO, L., ERÄNKÖ, O., AND JALAVISTO, E., *Acta Physiol. Scand.*, **17**, 130-49 (1948)
61. FOLKOW, B., AND UVNÄS, B., *Acta Physiol. Scand.*, **15**, 365-80 (1948)
62. FOLKOW, B., AND UVNÄS, B., *Acta Physiol. Scand.*, **15**, 389-400 (1949)
63. FOLKOW, B., HAEGER, K., AND UVNÄS, B., *Acta Physiol. Scand.*, **15**, 410-11 (1948)
64. FOLKOW, B., AND UVNÄS, B., *Acta Physiol. Scand.*, **16**, 191-94 (1949)
65. FOLKOW, B., FROST, J., HAEGER, K., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 195-200 (1949)
66. ARNOTT, W. M., AND MCFIE, J. M., *J. Physiol.*, (London) **107**, 233 (1948)
67. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 879-82 (1948)
68. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 603-6 (1948)
69. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 283-86 (1948)
70. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **143**, 239-42 (1949)
71. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 1363-66 (1948)
72. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 606-9 (1948)
73. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 780-82 (1948)
74. BINET, L., AND BURSTEIN, M., *Compt. rend.*, **221**, 197 (1945)
75. WALCOTT, W. W., AND DEYRUP, I. J., *Am. J. Physiol.*, **155**, 475 (1948)
76. MALMEJAC, J., AND CHARDON, G., *Compt. rend. soc. biol.*, **142**, 680-82 (1948)
77. SIEMS, L. L., AND KOSMAN, A. J., *Am. J. Physiol.*, **156**, 185-90 (1949)
78. BARCROFT, H., AND WALKER, A. J., *Lancet*, **I**, 1035-38 (1949)
79. BARCROFT, H., AND HAMILTON, G. T. C., *Lancet*, **I**, 441 (1948)
80. BARCROFT, H., AND HAMILTON, G. T. C., *Lancet*, **II**, 770-71 (1948)
81. MILLEN, J. W., *J. Anat.*, **82**, 68-80 (1948)
82. GREEN, R. S., IGLAUER, A., AND MCGUIRE, J., *J. Lab. Clin. Med.*, **33**, 951-60 (1948)
83. GREEN, R. S., IGLAUER, A., AND MCGUIRE, J., *J. Lab. Clin. Med.*, **33**, 1483-84 (1948)
84. HORVATH, S. M., AND BOTELHO, S. Y., *J. Applied Physiol.*, **1**, 586-96 (1949)
85. APPERLY, F. L., AND CARY, M. K., *Am. J. Med. Sci.*, **216**, 403-6 (1948)
86. DEITRICK, J. E., *Bull. N. Y. Acad. Med.*, **24**, 364-75 (1948)
87. BRITTON, S. W., *Am. J. Physiol.*, **156**, 1-11 (1949)
88. BRITTON, S. W., AND FRENCH, C. R., *Am. J. Physiol.*, **156**, 137-44 (1949)
89. HENRY, J. P., GAUER, O., MARTIN, E. E., KETY, S. S., AND KRAMER, K., *Federation Proc.*, **8**, 73 (1949)
90. SHAW, R. S., HENRY, J. P., GAMBLE, J. L., AND GAUER, O., *J. Applied Physiol.*, **1**, 441-47 (1948)
91. HERTZMAN, A. B., AND RANDALL, W. C., *J. Applied Physiol.*, **1**, 234-41 (1948)
92. PENNES, H. H., *J. Applied Physiol.*, **1**, 93 (1948)
93. BRECHT, K., AND PULFRICH, K., *Arch. ges. Physiol. (Pflügers)*, **249**, 609-18 (1947)
94. DE LALLA, V., AND BROWN, H. R., *Proc. Soc. Exptl. Biol. Med.*, **69**, 111-15 (1948)
95. MEAD, J., AND SCHOENFELD, R. C., *Federation Proc.*, **8**, 108 (1949)
96. KERSLAKE, D. M., *J. Physiol. (London)*, **108**, 451-57 (1949)

97. LANDOWNE, M., AND THOMPSON, W. N., *Proc. Soc. Exptl. Biol. Med.*, **69**, 537-42 (1948)
98. GUYTON, A. C., AND MILLER, G. L., *J. Lab. Clin. Med.*, **33**, 1450 (1948)
99. MERCKER, H., AND SCHOEDEL, W., *Arch. ges. Physiol. (Pflügers)*, **250**, 1-11 (1948)
100. JALAVISTO, E., MERTENS, O. AND SCHOEDEL, W., *Arch. ges. Physiol. (Pflügers)*, **249**, 368-76 (1947)
101. HILL, A. V., *J. Physiol. (London)*, **107**, 518-26 (1948)
102. BADER, M. E., AND MACHT, M. B., *J. Applied Physiol.*, **1**, 215-26 (1948)
103. COOPER, K. E., AND KERSLAKE, D. M., *J. Physiol. (London)*, **108**, 40P-41P (1949)
104. BADER, M. E., AND MEAD, J., *Federation Proc.*, **8**, 6-7 (1949)
105. PERKINS, J. F., LI, MAO-C., HOFFMAN, F., HOFFMAN, E., *Am. J. Physiol.*, **155**, 165-78 (1948)
106. BELDING, H. S., MEAD, J., AND BADER, M. E., *Federation Proc.*, **8**, 9-10 (1949)
107. BAZETT, H. C., LOVE, L., NEWTON, M., EISENBERG, L., AND FORSTER, R., *J. Applied Physiol.*, **1**, 3-19 (1948)
108. BAZETT, H. C., MENDELSON, E. S., LOVE, L., AND LIBET, B., *J. Applied Physiol.*, **1**, 169 (1948)
109. LOVE, L., *J. Applied Physiol.*, **1**, 20-34 (1948)
110. ASCHOFF, J., *Arch. ges. Physiol. (Pflügers)*, **249**, 148-66 (1947)
111. BRECHT, K., AND PULFRICH, K., *Arch. ges. Physiol. (Pflügers)*, **250**, 109-24 (1948)
112. KRAMER, K., AND SCHULZE, W., *Arch. ges. Physiol. (Pflügers)*, **250**, 141-70 (1948)
113. ASCHOFF, J., AND KAEMPFER, F., *Arch. ges. Physiol. (Pflügers)*, **249**, 112 (1947)
114. PAPPENHEIMER, J. R., EVERSOLE, S. L., AND SOTO-RIVERA, A., *Am. J. Physiol.*, **155**, 458 (1948)
115. HOWARTH, S., McMICHAEL, J., AND SHARPEY-SCHAFFER, E. P., *Clin. Sci.*, **6**, 247-55 (1948)
116. COHEN, S. M., EDHOLM, O. G., HOWARTH, S., McMICHAEL, J., AND SHARPEY-SCHAFFER, E. P., *Clin. Sci.*, **7**, 35 (1948)
117. BOUCKAERT, J. J., AND JOURDAN, E., *J. physiol.*, **41**, 69-114A (1949)
118. KETY, S. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 476-83 (1948)
119. KETY, S. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 484-92 (1948)
120. KETY, S. S., SHENKIN, H. A., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 493-99 (1948)
121. KETY, S. S., POLIS, B. D., NADLET, C. S., AND SCHMIDT, C. F., *J. Clin. Invest.*, **27**, 500-10 (1948)
122. KETY, S. S., HAFKENSCHIEL, J. H., JEFFERS, W. A., LEOPOLD, I. H., AND SHENKIN, H. A., *J. Clin. Invest.*, **27**, 511-14 (1948)
123. KETY, S. S., KING, B. D., HAFKENSCHIEL, J. H., HORVATH, S. M., AND JEFFERS, W. A., *J. Clin. Invest.*, **27**, 543 (1948)
124. SHENKIN, H. A., SCHEURMAN, W. G., SPITZ, E. B., AND GROFF, R. A., *Am. J. Med. Sci.*, **216**, 714-15 (1948)
125. MCCALL, M. L., *Am. J. Med. Sci.*, **216**, 596-97 (1948)
126. SJÖSTRAND, T., *Acta Physiol. Scand.*, **15**, 351-61 (1948)

127. POUPA, O., *Compt. rend. soc. biol.*, **142**, 1043-44 (1948)
128. NOELL, W., AND SCHNEIDER, M., *Arch. ges. Physiol. (Pflügers)*, **250**, 35-40 (1948)
129. HARMEL, M. H., HAFKENSCHIEL, J. H., AUSTIN, G. M., CRUMPTON, C. W., AND KETY, S. S., *J. Clin. Invest.*, **28**, 415 (1948)
130. GUYTON, A. C., *Am. J. Physiol.*, **154**, 45-54 (1948)
131. McDONALD, D. A., AND POTTER, J. M., *J. Physiol. (London)*, **108**, 34P (1949)
132. COOPER, K. E., GREENFIELD, A. D. M., AND HUGGETT, A. ST. G., *J. Physiol. (London)*, **108**, 160-66 (1949)
133. COOPER, K. E., AND GREENFIELD, A. D. M., *J. Physiol. (London)*, **108**, 167-76 (1949)
134. BARCROFT, J., *Researches on Pre-Natal Life* (1946), 104-11 (Basil Blackwell & Mott, Ltd., Oxford, 1946)
135. RICHINS, C. A., AND BRIZZEE, K., *J. Neurophysiol.*, **12**, 131-36 (1949)
136. BIZARD, G., VANLERENBERGHE, J., AND ROBELET, A., *Compt. rend. soc. biol.*, **142**, 660-62 (1948)
137. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *Compt. rend. soc. biol.*, **142**, 1031-32 (1948)
138. MYERS, J. D., AND HOLLAND, B. C., *J. Clin. Invest.*, **27**, 550-51 (1948)
139. MYERS, J. D., AND HICKAM, J. B., *J. Clin. Invest.*, **28**, 620-27 (1949)
140. ASHWORTH, M. A., AND HAIST, R. E., *Rev. can. biol.*, **7**, 177-78 (1948)
141. COHN, C., LEVINE, R., AND KOLINSKY, M., *Am. J. Physiol.*, **155**, 286-89 (1948)
142. CHAPMAN, C. B., HENSCHER, A., AND FORSGREN, A., *Proc. Soc. Exptl. Biol. Med.*, **69**, 170 (1948)
143. CHAPMAN, C. B., HENSCHER, A., MINCKLER, J., FORSGREN, A., AND KEYS, A., *J. Clin. Invest.*, **28**, 639-44 (1949)
144. SELKURT, E. E., HALL, P. W., AND SPENCER, M. P., *Am. J. Physiol.*, **156**, 40-46 (1949)
145. BLAKE, W. D., WEGRIA, R., KEATING, R. P., AND WARD, H. P., *Am. J. Physiol.*, **157**, 1-13 (1949)
146. BULL, G. M., *Clin. Sci.*, **7**, 77-108 (1948)
147. LITTLE, W. J., AVERA, J. W., AND HOOBLER, S. W., *Federation Proc.*, **8**, 98-99 (1949)
148. CALDWELL, F. T., ROLF, D., AND WHITE, H. L., *J. Applied Physiol.*, **1**, 597-600 (1949)
149. NISELL, O., *Acta Physiol. Scand.*, **16**, 121 (1948)
150. DONNET, V., ZWIRN, P., PRUNEYRE, A., AND MAFFRE, S., *Compt. rend. soc. biol.*, **143**, 88-89 (1949)
151. DONNET, V., ZWIRN, P., PRUNEYRE, A., AND MAFFRE, S., *Compt. rend. soc. biol.*, **143**, 89-90 (1949)
152. DONNET, V., ZWIRN, P., PRUNEYRE, A., AND MAFFRE, S., *Compt. rend. soc. biol.*, **143**, 91 (1949)
153. HELLEMS, H. K., HAYNES, F. W., DEXTER, L., AND KINNEY, J. D., *Am. J. Physiol.*, **155**, 98-105 (1948)
154. CHAMBERS, R., *Nature*, **162**, 835-36 (1948)
155. NICOLL, P. A., AND WEBB, R. L., *Am. J. Physiol.*, **155**, 456-57 (1948)

156. HALEY, T. J., AND HARRIS, D. H., *J. Pharmacol. Exptl. Therap.*, **95**, 293-302 (1949)
157. LASZT, L., *Helv. Physiol. et Pharmacol. Acta*, **7**, 192-206 (1949)
158. MOREL, F., AND MAROIS, M., *Compt. rend. soc. biol.*, **142**, 1366-59 (1948)
159. SILVER, A. F., *Am. J. Physiol.*, **154**, 16-18 (1948)
160. SILVER, A. F., AND REED, C. I., *Am. J. Physiol.*, **154**, 19-26 (1948)
161. ELSTER, S. K., FREEMAN, M. E., AND DORFMAN, A., *Am. J. Physiol.*, **156**, 429-32 (1949)
162. STURM, H., *Arch. ges. Physiol. (Pflügers)*, **249**, 480-93 (1947)
163. LAZARUS, S., MUNRO, H. N., AND BELL, G. H., *Clin. Sci.*, **7**, 175 (1948)
164. POLLACK, A. A., AND WOOD, E. H., *J. Applied Physiol.*, **1**, 649-62 (1949)
165. POLLACK, A. A., TAYLOR, B. E., MYERS, T. T., AND WOOD, E. H., *J. Clin. Invest.*, **28**, 559-63 (1949)
166. HICKAM, J. B., MCCULLOUGH, R. P., AND REEVES, R. J., *Am. Heart J.*, **37**, 1017-23 (1949)
167. TICHY, V. L., AND SHAW, B. M., *Proc. Soc. Exptl. Biol.*, **69**, 368-69 (1948)
168. VOLWILER, W., GRINDLAY, J. H., AND BOLLMAN, J. L., *Am. J. Physiol.*, **155**, 474 (1948)
169. LEVY, L. K., AND BURCH, G. E., *Ann. Internal. Med.*, **29**, 174-77 (1948)
170. CORBOZ, J. R., *Helv. Physiol. et Pharmacol. Acta*, **6**, 55-67 (1948)
171. CORBOZ, J. R., *Helv. Physiol. et Pharmacol. Acta*, **6**, 247-57 (1948)
172. FREIS, E. D., STANTON, J. R., AND EMERSON, C. P., *Am. J. Physiol.*, **157**, 153-57 (1949)
173. MILLER, B. J., *J. Lab. Clin. Med.*, **33**, 910-18 (1948)
174. SCHLICHTER, J. G., WILBURNE, M., AND GROSSMAN, M., *Am. J. Med. Sci.*, **216**, 523-27 (1948)
175. STANTON, J. R., FREIS, E. D., AND WILKINS, R. W., *J. Clin. Invest.*, **28**, 553-58 (1949)
176. WRIGHT, H. P., OSBORN, S. B., AND EDMONDS, D. G., *Lancet*, **II**, 757-79 (1948)
177. GILLESPIE, E. C., AND REYNOLDS, S. R. M., *Proc. Soc. Exptl. Biol. Med.*, **70**, 721-24 (1949)
178. OGDEN, E., CLOUSE, P. A., AND MURRAY, R. V., *Am. J. Physiol.*, **155**, 457 (1948)
179. ZERAHN, K., *Acta Physiol. Scand.*, **16**, 117-20 (1948)
180. ALLEN, T. H., AND ORAHOVATS, P. D., *Am. J. Physiol.*, **154**, 27-37 (1948)
181. SJÖSTRAND, T., *Acta Physiol. Scand.*, **16**, 211 (1948)
182. ROSENTHAL, R. L., AND TOBIAS, C. W., *J. Lab. Clin. Med.*, **33**, 1110-22 (1948)
183. MENDLOWITZ, M., *Bull. U. S. Army Med. Dept.*, **8**, 58 (1948)
184. McLAIN, P. L., AND RUHE, C. H. W., *Am. J. Physiol.*, **156**, 12-17 (1949)
185. EDERSTROM, H. E., *Proc. Soc. Exptl. Biol. Med.*, **70**, 172-73 (1949)
186. BARNES, D. W. H., LOUTIT, J. F., AND REEVE, E. B., *Clin. Sci.*, **7**, 135-54 (1948)
187. BARNES, D. W. H., LOUTIT, J. F., AND REEVE, E. B., *Clin. Sci.*, **7**, 155-73 (1948)
188. KELLY, F. J., SIMONSEN, D. H., AND ELMAN, R., *J. Clin. Invest.*, **27**, 795-804 (1948)

189. KRIEGER, H., STORAASLI, J. P., FRIEDEL, H. L., AND HOLDEN, W. D., *Proc. Soc. Exptl. Biol. Med.*, **68**, 511-15 (1948)
190. MAYERSON, H. S., LYONS, C., PARSON, W., NIESET, R. T., AND TRAUTMAN, W. V., *Am. J. Physiol.*, **155**, 232-38 (1948)
191. NIESET, R. T., PORTER, B., TRAUTMAN, W. V., BELL, R. M., PARSON, W., LYONS, C., AND MAYERSON, H. S., *Am. J. Physiol.*, **155**, 226-32 (1948)
192. REEVE, E. B., AND VEALL, N., *J. Physiol. (London)*, **108**, 12-23 (1949)
193. HAMILTON, H. E., SHEETS, R. F., AND DE GOWIN, E. L., *J. Lab. Clin. Med.*, **33**, 1650-51 (1948)
194. NIZET, A., *Quart. J. Exptl. Physiol.*, **34**, 123-28 (1948)
195. McLAIN, P. L., RUHE, C. H. W., AND KRUSE, T. K. T., *Federation Proc.*, **8**, 102-3 (1949)
196. COURTICE, F. C., AND GUNTON, R. W., *J. Physiol. (London)*, **108**, 142-56 (1949)
197. CULLUMBINE, H., AND KOCH, A. C. E., *Quart. J. Exptl. Physiol.*, **35**, 39-46 (1949)
198. COURTICE, F. C., AND GUNTON, R. W., *J. Physiol. (London)*, **108**, 405-17 (1949)
199. COURTICE, F. C., AND GUNTON, R. W., *J. Physiol. (London)*, **108**, 418-26 (1949)
200. ROSSITER, R. J., *Lancet*, **I**, 222-23 (1949)
201. NYLIN, G., AND HEDLUND, D. S., *Am. Heart J.*, **37**, 543-50 (1949)
202. COHN, J. E., AND SHOCK, N. W., *Am. J. Med. Sci.*, **217**, 388-91 (1949)
203. WANG, C. F., AND HEGSTED, D. M., *Am. J. Physiol.*, **156**, 218-26 (1949)
204. BRAUN-MENENDEZ, E., AND COVIAN, M. R., *Compt. rend. soc. biol.*, **142**, 1158-59 (1948)
205. PARSON, W., MAYERSON, H. S., LYONS, C., PORTER, B., AND TRAUTMAN, W. V., *Am. J. Physiol.*, **155**, 239-41 (1948)
206. SPEALMAN, C. R., BIXBY, E. W., WILEY, J. L., AND NEWTON, M., *J. Applied Physiol.*, **1**, 242-53 (1948)
207. POST, R. L., AND SPEALMAN, C. R., *J. Applied Physiol.*, **1**, 227-33 (1948)
208. HENRY, J. P., HENDRICKSON, I., MOVITT, E., AND MEEHAN, J. P., *J. Clin. Invest.*, **27**, 700-5 (1948)
209. ALTSCHULE, M. D., AND CLINE, J. E., *Proc. Soc. Exptl. Biol. Med.*, **69**, 598-601 (1948)
210. PICKERING, R. W., AND DOW, P., *Federation Proc.*, **8**, 127 (1949)
211. GLASSER, O., AND PAGE, I. H., *Am. J. Physiol.*, **154**, 297-315 (1948)
212. REMINGTON, J. W., WHEELER, N. C., BOYD, G. H., AND CADDELL, H. M., *Proc. Soc. Exptl. Biol. Med.*, **69**, 150-51 (1948)
213. EDHOLM, O. G., *Federation Proc.*, **8**, 39 (1949)
214. ALLISON, J. B., COLE, W. H., WALCOTT, W. W., GELFAN, S., ROOT, W. S., AND GREGERSEN, M. I., *Am. J. Physiol.*, **156**, 191-201 (1949)
215. NASTUK, W. L., AND BEATTY, C. H., *Am. J. Physiol.*, **156**, 202-9 (1949)
216. NASTUK, W. L., AND BEATTY, C. H., *Am. J. Physiol.*, **156**, 210-17 (1949)
217. BEATTY, C. H., *Am. J. Physiol.*, **154**, 107-18 (1948)
218. KLINE, D. L., *Am. J. Physiol.*, **154**, 87-93 (1948)
219. MAZUR, A., AND SHORR, E., *J. Biol. Chem.*, **176**, 771-88 (1948)
220. BAEZ, S., MAZUR, A., AND SHORR, E., *Federation Proc.*, **8**, 7 (1949)

221. CORCORAN, A. C., MASSON, G., AND SCHAFFENBURG, C., *Federation Proc.*, **8**, 28-29 (1949)
222. REINHARD, J. J., GLASSER, O., AND PAGE, I. H., *Am. J. Physiol.*, **155**, 106-13 (1948)
223. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *Compt. rend. soc. biol.*, **142**, 378-80 (1948)
224. RAU, C. G., *Am. J. Physiol.*, **156**, 454-57 (1949)
225. FELDMAN, M., RODBARD, S., AND KATZ, L. N., *Am. J. Physiol.*, **154**, 391-96 (1948)
226. VAN LOO, A., SURTSHIN, A., AND KATZ, L. N., *Am. J. Physiol.*, **154**, 397-404 (1948)
227. MARSH, D. F., AND VAN LIERE, E. J., *J. Pharmacol. Exptl. Therap.*, **94**, 221-31 (1948)
228. GÖPFERT, H., *Arch. ges. Physiol. (Pflügers)*, **249**, 109-229 (1947)
229. BINET, L., BURSTEIN, M., AND LEMAIRE, R., *Compt. rend. soc. biol.*, **142**, 801-3 (1948)
230. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 1204-6 (1948)
231. MALMEJAC, J., CHARDON, G., AND GROSS, A., *Compt. rend. soc. biol.*, **142**, 678-80 (1948)
232. MALMEJAC, J., CHARDON, G., AND GROSS, A., *Compt. rend. soc. biol.*, **142**, 682 (1948)
233. MALMEJAC, J., CHARDON, G., AND GROSS, A., *Compt. rend. soc. biol.*, **142**, 1102-9 (1948)
234. KRAMER, K., AND LUFT, U. C., *Federation Proc.*, **8**, 88-89 (1949)
235. BONSDORFF, E., AND JALAVISTO, E., *Acta Physiol. Scand.*, **16**, 150-70 (1948)
236. GRANDJEAN, E., *Helv. Physiol. et Pharmacol. Acta*, **6**, 574-83 (1948)
237. FRANK, E., AND WEZLER, K., *Arch. ges. Physiol. (Pflügers)*, **250**, 598-622 (1948)
238. WEZLER, K., AND FRANK, E., *Arch. ges. Physiol. (Pflügers)*, **250**, 249-75 (1948)
239. EULER, U. S. V., *Acta Physiol. Scand.*, **16**, 63 (1948)
240. EULER, U. S. V., AND ÅSTRÖM, A., *Acta Physiol. Scand.*, **16**, 97 (1948)
241. PEART, W. S., *J. Physiol. (London)*, **108**, 491-501 (1949)
242. HOLTON, P., *J. Physiol. (London)*, **108**, 525-29 (1949)
243. GOLDENBERG, M., FABER, M., ALSTON, E. J., AND CHARGAFF, E. C., *Science*, **109**, 534-55 (1949)
244. TULLAR, B. F., *Science*, **109**, 536-37 (1949)
245. AUERBACH, M. E., AND ANGELL, E., *Science*, **109**, 537-38 (1949)
246. FOLKOW, B., FROST, J., AND UVNÄS, B., *Acta Physiol. Scand.*, **15**, 412-20 (1948)
247. GOLDENBERG, M., PINES, K. L., BALDWIN, E. DE F., GREENE, D. G., AND ROH, C. E., *Am. J. Med.*, **5**, 792-806 (1948)
248. BARCROFT, H., AND KONZETT, H., *Helv. Physiol. et Pharmacol. Acta*, **7**, C4-5 (1949)
249. BARCROFT, H., AND KONZETT, H., *Lancet*, **I**, 147-48 (1949)
250. DUNCANSON, D., STEWART, T., AND EDHOLM, O. G., *Federation Proc.*, **8**, 37 (1949)
251. MEIER, R., AND BEIN, H. J., *Experientia*, **4**, 358 (1948)
252. WEST, G. B., *Brit. J. Pharmacol.*, **3**, 189-97 (1948)

253. WEST, G. B., *Brit. J. Pharmacol.*, **4**, 63-67 (1949)
254. GRAHAM, J. D. F., *J. Physiol. (London)*, **108**, 15P (1949)
255. GRAHAM, J. D. P., *J. Pharm. Pharmacol.*, **1**, 17-27 (1949)
256. ROTHLIN, E., *Experientia*, **5**, 78 (1949)
257. BOER, J. DE, VAN DONGEN, K., *Arch. intern. pharmacodynamie*, **77**, 434-41 (1948)
258. GOETZ, R. H., *Lancet*, **I**, 510-14 (1949)
259. HAYES, D. W., WAKIM, K. G., HORTON, B. T., AND PETERS, G. A., *J. Lab. Clin. Med.*, **33**, 1479 (1948)
260. MOE, G. K., RENNICK, B. R., CAPO, L. R., AND MARSHALL, M. R., *Am. J. Physiol.*, **157**, 158-67 (1949)
261. RELMAN, A. S., AND EPSTEIN, F. H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 11-14 (1949)
262. GREEN, H. D., AND OGLE, B. C., *J. Applied Physiol.*, **1**, 663-69 (1949)
263. PEARL, F. L., *Ann. Surg.*, **128**, 1092-99 (1948)
264. PEARL, F. L., *Ann. Surg.*, **128**, 1100 (1948)
265. PAGE, I. H., PRINCE, R., AND REINHARD, J. J., *Federation Proc.*, **8**, 437 (1949)
266. MORRISON, J. L., AND FARRAR, C. H., *Proc. Soc. Exptl. Biol. Med.*, **71**, 235-37 (1949)
267. HOOBLER, S. W., AVERA, J. W., LITTLE, W. J., PEET, M. M., AND BASSETT, R. C., *Federation Proc.*, **8**, 77 (1949)
268. SEED, J. C., AND MCKAY, E. A., *Proc. Soc. Exptl. Biol. Med.*, **70**, 724-26 (1949)
269. GOLLWITZER-MEIER, K., *Arch. ges. Physiol. (Pflügers)*, **249**, 44 (1947)
270. BÜLBRING, E., AND BURN, J. H., *J. Physiol. (London)*, **108**, 6P (1949)
271. WAKIM, K. G., PETERS, G. A., TERRIER, J. C., AND HORTON, B. T., *J. Lab. Clin. Med.*, **34**, 380-86 (1949)
272. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 138-40 (1948)
273. WEBER, R. P., AND STEGGERDA, F. R., *Proc. Soc. Exptl. Biol. Med.*, **70**, 261-63 (1949)
274. MACHT, M. B., *J. Clin. Invest.*, **27**, 454-62 (1948)
275. HOLMSTEDT, B., AND WRETILIND, K. A. J., *Acta Physiol. Scand.*, **16**, 321 (1949)
276. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **142**, 1487-88 (1948)
277. SAPEIKA, N., *Arch. Internal. Med.*, **82**, 263-309 (1948)
278. SMIRK, F. H., *Brit. Med. J.*, **I**, 791-99 (1949)
279. PAGE, I. H., *Bull. U. S. Army Med. Dept.*, **8**, 367-72 (1948)
280. KILPATRICK, J. A., *Brit. Heart J.*, **10**, 48 (1948)
281. GREEN, D. M., COLEMAN, D. H., AND MCCABE, M., *Am. J. Physiol.*, **154**, 465-74 (1948)
282. GREEN, D. M., *J. Lab. Clin. Med.*, **33**, 853 (1948)
283. SKAHEN, J. G., AND GREEN, D. M., *Am. J. Physiol.*, **155**, 290-94 (1948)
284. FRIEDMAN, S. M., FRIEDMAN, C. L., AND CAMPBELL, C. G., *Am. J. Physiol.*, **157**, 241-47 (1949)
285. FRIEDMAN, S. M., AND FRIEDMAN, C. L., *J. Exptl. Med.*, **89**, 631-42 (1949)
286. SUMMERS, J. E., *Am. J. Physiol.*, **154**, 119-21 (1948)
287. DAVIS, W. D., SEGALOFF, A., AND JACOBS, W., *J. Lab. Clin. Med.*, **33**, 1483 (1948)

288. GOLDMAN, M. L., AND SCHROEDER, H. A., *Am. J. Med.*, **5**, 33-39 (1948)
289. BLACK, D. A. K., PLATT, R., ROWLANDS, E. N., AND VARLEY, H., *Clin. Sci.*, **6**, 295 (1948)
290. GROLLMAN, A., MUIRHEAD, E. E., AND VANATTA, J., *Am. J. Physiol.*, **157**, 21-30 (1949)
291. DE LA BARREDA, P., DE MOLINA, A. F., AND JIMENEZ DIAZ, C., *Bull. Inst. Med. Research*, **1**, 53-63 (1948)
292. BRAUN-MENENDEZ, E., AND COVIAN, M. R., *Compt. rend. soc. biol.*, **142**, 1569-70 (1948)
293. SCHROEDER, H. A., GOLDMAN, M. L., AND OLSEN, N. S., *J. Clin. Invest.*, **27**, 555 (1948)
294. GOLDMAN, M. L., KRISS, J. P., FITCHER, P. H., AND SCHROEDER, H. A., *Am. J. Med. Sci.*, **217**, 637-43 (1949)
295. GOLLAN, F., RICHARDSON, E., AND GOLDBLATT, H., *J. Exptl. Med.*, **88**, 389-400 (1948)
296. FLASHER, J., *Federation Proc.*, **8**, 87 (1949)
297. OGDEN, E., TRIPP, E., COLLINGS, W. D., AND VICTOR, J., *Texas Repts. Biol. Med.*, **6**, 364-72 (1948)
298. CANHAM, R. G., AND WAKERLIN, G. E., *Am. J. Physiol.*, **155**, 430 (1948)
299. YEAKEL, E. H., SHENKIN, H. A., ROTHBALLER, A. B., AND McCANN, S. M., *Am. J. Physiol.*, **155**, 118-27 (1948)
300. McCANN, S. M., ROTHBALLER, A. B., YEAKEL, E. H., AND SHENKIN, H. A., *Am. J. Physiol.*, **155**, 128-31 (1948)
301. EVANS, J. A., AND BARTELS, C. C., *Ann. Internal Med.*, **30**, 307-29 (1949)
302. SMITHWICK, R. H., *Brit. Med. J.*, **II**, 237 (1949)
303. GRIMSON, K. S., AND ORGAIN, E. S., *J. Clin. Invest.*, **27**, 537 (1948)
304. WILKINS, R. W., CULBERTSON, J. W., AND HALPERIN, M. H., *Ann. Internal Med.*, **30**, 291-306 (1949)
305. WOLF, S., PFEIFFER, J. P., RIPLEY, H. S., WINTER, O. S., AND WOLFF, H., *Ann. Internal Med.*, **29**, 1056-76 (1948)
306. BOLOMEY, A. A., MICHIE, A. J., MICHIE, C., BREED, E. S., SCHREINER, G. E., AND LAUSON, H. D., *J. Clin. Invest.*, **28**, 10-17 (1949)
307. LANDOWNE, M., ALVING, A. S., AND ADAMS, W., *J. Clin. Invest.*, **27**, 546 (1948)
308. TAYLOR, R. D., BIRCHALL, R., CORCORAN, A. C., AND PAGE, I. H., *Am. Heart J.*, **36**, 22-25 (1948)
309. CORCORAN, A. C., TAYLOR, R. D., AND PAGE, I. H., *Am. Heart J.*, **36**, 226-40 (1948)
310. HARDGROVE, M., AND MENDELSON, D. J., *J. Lab. Clin. Med.*, **33**, 1496 (1948)
311. NICKERSON, M., BULLOCK, F., AND NOMAGUCHI, G. M., *Proc. Soc. Exptl. Biol. Med.*, **68**, 425-31 (1948)
312. PAGE, I. H., AND TAYLOR, R. D., *Am. J. Physiol.*, **156**, 412-21 (1949)
313. STEAD, W. W., REISER, M. F., RAPOPORT, S., AND FERRIS, E. B., *J. Clin. Invest.*, **27**, 766-77 (1948)
314. SOLOFF, L. A., BURNETT, W. E., AND BELLO, C. T., *Am. J. Med. Sci.*, **216**, 665-72 (1948)
315. FREW, J. L., AND ROSENHEIM, M. L., *Clin. Sci.*, **7**, 217 (1949)

## HEART

BY ALBERT HEMINGWAY<sup>1</sup>

*Department of Physiology, School of Medicine,  
University of Leeds, England*

The present review covers the period July 1948 to June 1949 with some earlier papers not previously reviewed. The selection of topics and papers has been arbitrary and limited by the available space; it must represent to some extent the interests of the reviewer.

### DYNAMICS OF THE HEART BEAT

*Timing of the events of the cardiac cycle.*—In the dog, Remington, Hamilton & Alquist (1) showed that during rapid changes in cycle length the duration of the ejection phase was determined not only by the rate but also by the venous filling and the peripheral resistance. The ejection phase was prolonged when the heart was stimulated to do more work by ephedrine or Prisol. Length of systole showed a better correlation with stroke volume and with left ventricular work than with cycle length. Schlapp & Walker (2) demonstrated in man that during a respiratory cycle the duration of systole increased as the arterial blood pressure rose.

Interest in congenital defects of the heart seems to have stimulated activity and given opportunity for timing the order of events. Coblentz *et al.* (3) simultaneously recorded pressures in the right atrium, right ventricle, pulmonary artery, brachial artery, and the electrocardiogram. They have correlated more closely the mechanical and electrical events than has previously been done in man. On some occasions a double lumen catheter was used to record simultaneously the pressures in the right atrium and the right ventricle or in the right ventricle and the pulmonary artery. The intervals between various events of the cardiac cycle and their duration were measured. Although such measurements have previously been made on animals, as in the classical work of Lewis, they have remained until now largely inferential in man. In general, the intervals between the electrical and the corresponding mechanical events were about three times longer in man than in the dog. Pulmonary hypertension was observed in some children

<sup>1</sup> My thanks are due to my secretary, Miss J. C. King, for her assistance in compiling the material for this review.

with congenital heart disease and there was an associated lengthening of the isometric contraction phase, but despite the hypertrophy and dilatation which occurs in patients of this type there was no lengthening of the interval between the beginning of the Q wave of the electrocardiogram and the onset of right ventricular systole. In a patient with a ventricular septal defect there was an opportunity simultaneously to measure pressures in both ventricles. The two systoles began together. But in cases of premature ventricular contraction the ventricles contracted asynchronously according to the place of origin of the ectopic beat and were not always effective in expelling blood. Risk of damage makes direct catheterization of the left ventricle impracticable according to Hellems *et al.* (4).

Boone *et al.* (5) used the electrokymograph to follow changes in outline of the heart in conjunction with recordings of the heart sounds and arterial pulse pressures. The duration of the isometric relaxation phase was 0.06 to 0.16 sec. in normal subjects but it was increased in cases of hypertension.

*Pressures in the chambers of the heart.*—The development of manometric instruments which possess little inertia and operate on small volume changes has continued [Rappaport & Sarnoff (6); Pritchard *et al.* (7); Peterson, Dripps & Risman (8); Tompkins (9)].

Lagerlof & Werko (10) used a critically damped electrical manometer to measure pressures in the human heart. Typical results were: brachial artery, 132/80, mean 100; pulmonary artery, 23/8, mean 15; right ventricle, 24/4, mean 9; right atrium, mean 2.8 mm. Hg. These values were confirmed by Battro *et al.* (11), who also investigated the effects produced by respiratory movements. In chronic pulmonary disease the elasticity of the lungs and the peripheral resistance in the pulmonary circuit modified the respiratory variations. In heart failure and atrial fibrillation the pressures in the right side of the heart were elevated and there was no respiratory variation probably because of the distension of the right side of the heart. Modified Valsalva's experiments were performed on dogs by Sarnoff *et al.* (12). During the "overshoot" immediately following the deflation of the lungs, right ventricular pressure rose above 70 mm Hg.

A number of papers suggest to the reviewer the need for caution in drawing inferences from atrial pressure measurements and,

particularly, in relating right atrial pressures to the working of the left ventricle. Opdyke *et al.* (13, 14) compared pressures in the atria in various circumstances in dogs. Events were rarely synchronous and the pressure in the left atrium was usually greater than the pressure in the right except at the beginning of right atrial systole when the pressures were equal. Occasionally, however, the gradient of pressure was reversed for a brief period. Intravenous infusion caused a rise in pressure in both atria but greater in the left; haemorrhage decreased left atrial pressure more than the right. It was concluded that the left atriovenous system is less distensible than the right. Hence, if atrial inflow is fairly constant the pressure within the atrial cavity will vary in accordance with the outflow, i.e., with ventricular filling, and with the volume-elasticity characteristics of the atriovenous system, and will be determined by the dynamic balance between these factors. This is a consideration which should not be ignored by those investigating the relationship between right atrial pressure and cardiac output. Martin & Essex (15) reported findings similar to those of Opdyke *et al.* and showed, as did Little, Hawley & Opdyke (16), that the atrial pressure difference persisted even after the induction of interatrial septal defects. There seem to be similar pressure relationships in the cat and they can be modified by the action of drugs. Quinidine (15 to 30 mg. per kg.) produces myocardial impairment and right atrial pressure rises above the left; epinephrine causes a rise in left atrial pressure by a direct (inotropic) action on the myocardium according to Reiss & DiPalma (17).

The rise in right atrial pressure caused by an increased venous inflow in the heart-lung preparation has been used by Wollenberger & Kraye (18) to assess the negative inotropic action of some central nervous depressants and some local anaesthetics, while Woods *et al.* (19) have used a similar method to compare the cardiac toxicity of thiobarbiturates.

Congenital defects of the interventricular septum have been simulated by the establishment by Dillon & Schreiber (20) of an experimental connection between the ventricles. Although the experimental findings may be criticized because of the apparently hypodynamic condition of the heart, it seems that the right ventricle is sufficiently distended at the end of diastole to be able to expel into the pulmonary artery the blood which it receives from the right atrium during diastole and from the left ventricle via the

shunt during systole. The pressure gradient between the ventricles is diminished by the fall in left ventricular pressure and the rise in right ventricular pressure. The increase in left ventricular diastolic pressure is attributed to the greater output from the right ventricle through the unchanged resistance of the pulmonary vascular bed.

*Pulmonary circulation.*—The pulmonary vascular bed usually has a low resistance. Rodbard & Brown (21) have commented on the low pulmonary arterial pressure found in all vertebrates, and Hellemis *et al.* (4) have estimated the pulmonary capillary pressure in dogs to be 8.3 (5.5 to 10.0) mm. Hg.

After resection of one lung in man the pulmonary arterial pressure rose during exercise; in the normal subject the pressure fell or was unchanged [Cournand, Riley & Himmelstein (22)]. Borden, Wilson & Ebert (23) found no difference between the cardiac output in normal subjects and those with chronic pulmonary emphysema but pulmonary arterial pressure was about 50 per cent higher in the latter.

Griswold *et al.* (24) investigated pulmonary hypertension in congenital heart disease. Pulmonary peripheral resistance at rest is higher than normal but is lowered during exercise. Taylor *et al.* (25) and Grover, Swann & Maaske (26) observed that the mean drop in pulmonary pressure on closure of a patent ductus arteriosus was 11 mm. Hg.

*Circulation time and radiocardiography.*—Although there are a number of reports about the measurement of circulation times with the oximeter, e.g. Wood, Taylor & Knutson (27) and other methods, the most significant advance in this field seems to be the introduction of radiocardiography by Prinzmetal *et al.* (28). They injected rapidly 0.1 to 0.2 m.C Na<sup>24</sup> intravenously (preferably by catheter) and recorded the passage through the heart with a shielded Geiger-Müller counter placed over the precordium. Separate waves indicated the passage through each ventricle in turn and the clearing of the left ventricle was followed.

*Cardiac output: methods of measurement.*—Although the application of the principle of Fick through catheterization of the right heart is probably the most accurate method of estimating cardiac output in man, the inherent difficulties have stimulated the search for other methods which can be applied repeatedly and frequently

to the same subject under conditions giving freedom of position and movement. The ideal method has not been found.

Duomarco, Dillon & Wiggers (29) did not get good agreement between the method of Hamilton & Remington (30), which employs measurement of pulse pressure and arterial extensibility, and direct measurement of the input into the right and left ventricles.

The direct Fick method has again been compared with the acetylene method by Werko & Lagerlof (31) and by Werko, Berseus & Lagerlof (32). Their findings are of general interest to those using indirect methods. The actual rebreathing procedure of the acetylene method does not alter the cardiac output, as assessed by constancy of the arteriovenous oxygen difference; but samples of the blood from the pulmonary artery showed that small amounts of acetylene were recirculating within 10 to 15 sec. and larger amounts within 15 to 20 sec. Indirect methods are most likely to be satisfactory when the circulation time is long.

Tanner (33) concluded from a statistical comparison that the direct Fick and the ballistocardiograph methods are more reliable than the acetylene and ethyl iodide methods. He criticizes the use of cardiac indices based on one measurement, e.g. surface area, and suggests the use of multiple regression equations, making allowance for size, age, and heart rate. The interpretation of the ballistocardiogram is still unsettled and Nickerson (34) has used a model to show the alterations from normal which are likely to occur in coarctation of the aorta or in shock.

Morrissey & Palmer (35) have introduced mechanical methods to take the samples of air required for an indirect Fick method using carbon dioxide. In 12 normal subjects the cardiac index was 2.0 to 3.7 l. per sq. m. per min. and very little co-operation was wanted from the subject.

The electrokymograph was employed by Ring, Balaban & Oppenheimer (36) to estimate changes in the density of the heart during a cardiac cycle and after appropriate calibrations the stroke volume was calculated. Meier, Tripod & Wirz (37) applied the principle of the oximeter to measure the cardiac output in rabbits by a direct Fick method.

*Conditions affecting cardiac output.*—Seely (38) investigated the effects of the respiratory cycle on the output of the ventricles by accurate measurements of intrathoracic, aortic, and right

atrial pressures. With fairly short and shallow inspiration no increase in right atrial pressure or right ventricular stroke volume could be inferred but during prolonged and deep inspirations there were signs of increased cardiac output although again there was no demonstrable change in right atrial pressure. It is possible that the volume-elasticity coefficient of the right atrium permits increased filling without any measurable rise of atrial pressure.

Apprehension may affect the cardiac output during catheterisation but May *et al.* (39) stated that its effect is abolished by high spinal anaesthesia. Sedation may, therefore, be necessary in routine use to obtain a true resting value. Employment of such a precaution might have prevented the high cardiac outputs which were measured by Bolomey *et al.* (40) at the same time as renal blood flows were being assessed. No difference in cardiac indices was found between normal subjects and those from a group with essential hypertension, although the effective renal blood flow was smaller in the latter group.

Werko & Lagerlof (31) found the cardiac output, by catheterisation, to be about 10 per cent higher in early pregnancy and 10 to 20 per cent lower in late pregnancy than in normal nonpregnant women.

Riley *et al.* (41) have notably confirmed by catheterisation studies the conception that there is an approximately linear relationship between cardiac output and oxygen uptake during exercise. The relationship was similar in cases of pulmonary disease but the outputs were limited. The cardiac output of athletes and nonathletes was increased when working on the cycle ergometer or during the step test, but the athlete's output increased more than the nonathlete's particularly during the bicycle tests, according to Peterson *et al.* (42).

Cohen *et al.* (43) examined subjects with peripheral arterio-venous aneurysms. Cardiac output was increased (2.2 to 4.5 l. per min. per 100 ml. oxygen uptake; highest output, 16 l. per min.) and venous filling pressure and heart rate were usually higher than normal. When the shunt was closed by manual pressure, the cardiac output was reduced but did not reach the usual normal level; but patients studied one to two months after closure by operation had a lower output than immediately after closure by compression. Administration of atropine (2 mg. intravenously) increased the rate and the output although the atrial pressure fell.

Arteriovenous aneurysm of the lung is not as rare as is thought and may be confused with a congenital heart defect. Baker & Trounce (44) described two cases. In one the right ventricular output was 12 l. per min. of which 9.4 l. passed through the shunt. Stotz (45) described cases of traumatic arteriovenous aneurysm of twenty years' duration who showed little cardiac disability although in some others heart failure occurred.

The alterations in cardiac output and its distribution to various parts of the body during acute anoxaemia have been investigated by Feldman, Rodbard & Katz (46). About 75 sec. after the onset of anoxaemia there was very little blood return through the inferior vena cava but the superior vena flow was increased and remained so until the heart began to fail.

*Venous blood pressure and venous return.*—Venous blood pressure measured peripherally may be indicative of the pressure gradient to the heart or, taken in conjunction with measurements in central veins, may denote the balance between the rate of venous return and the ability of the heart to adjust its output correspondingly.

Irwin & Winsor (47) measured the pressure in the antecubital vein in children aged three to ten years. The pressure increased with age but the mean was  $54.3 \pm 17.1$  mm. H<sub>2</sub>O. The pressure was higher (92.7 mm. H<sub>2</sub>O) in one group with rheumatic heart disease who did not, however, show any clinical signs of congestion, and in another group with acute glomerulonephritis the pressure was 97.3 mm. Venous pressure at the ankle was measured by Pollack, Taylor & Myers (48), and with the subject standing the pressure was equal to a column of blood reaching to the third intercostal space. During walking, the pumping action of the muscles reduced the pressure to 23 mm. Hg. A much smaller fall was observed when the venous valves were incompetent. The effects of negative and positive acceleration on the venous return to the heart and the consequent changes in arterial blood pressure and distribution have been investigated by Shaw *et al.* (49) and Britton (50).

The question whether part of the therapeutic effect produced by digitalis in heart failure is due to an action on the veins was investigated by Wood & Paulett (51), who decided that the action is primarily on the heart.

*Size of the heart.*—Maresch (52) found that cardiac diameter, measured by x-rays, increases at about the same rate as the body

as a whole. Linzbach (53) postulated a constant number of fibres in the heart, which, according to Lowe & Bate (54), were the same size in different layers of the heart. Hypertrophy affected all the fibres similarly. Walls (55) found that the fibres of the rabbit heart destroyed by burning do not regenerate.

The technique of angiocardiology is discussed in the papers of Dotter & Steinberg (56); Brocklebank (57); Keele (58); and Carson *et al.* (59). Burford & Carson (60) described a method for retrograde filling of the aorta and its branches from the common carotid artery, and Sutton, Wendel & Grant (61) stressed the advantages of injecting contrast media directly into the right heart by catheterization.

Hamilton & Dow (62) have derived a new formula for measuring heart volume from x-ray shadow area, and Kay *et al.* (63) have demonstrated the possibility of following alterations in the size of the aorta and pulmonary artery by electrokymography.

#### HEART RATE AND CARDIAC REFLEXES

*Innervation of the heart.*—Unilateral removal of the second to fifth thoracic sympathetic ganglia leads to some slowing of the heart and diminishes the response to exercise. Although there is considerable individual variation, section of the right side seems to have a greater effect on the heart rate than section of the left according to Chapman *et al.* (64).

The nature of the transmitter which may be released at the sympathetic postganglionic nerve endings has been further investigated. In the experiments of Folkow *et al.* (65) stimulation of the stellate ganglion in the cat and dog was followed by the appearance of an acetylcholine-like substance in coronary perfusate.

Intravenous infusion of norepinephrine (5 to 10  $\mu$ g. per min. and occasionally 2  $\mu$ g.) causes slowing of the heart [Goldenberg *et al.* (66); Duncanson, Stewart & Edholm (67)]. Barcroft & Konzett (68) attribute the slowing to reflex activity consequent on peripheral vasoconstriction caused by norepinephrine.

Constant, Adronis & Ogden (69) have reiterated that modifications in cardiovascular reactions are caused by anaesthetics.

*Reflexogenic regions.*—Interest has continued in the possibility of reflexes originating in the ventricles. Freis *et al.* (70) reported that the veratrum alkaloids produced bradycardia in man. Cardiac

output was unchanged in normal subjects but was sometimes increased in cases of venous congestion. Aviado & Pontius (71) found that the bradycardia caused by veratridine injections depended on the concentration in the coronary arteries.

Emmelin & Feldberg (72) investigated the slowing of the heart caused by intravenous injection of adenosinetriphosphate (ATP). In cats, the slowing was due chiefly to a reflex with both afferent and efferent pathways in the vagus, although there may have been some direct action on the cardioinhibitory centre. The reflex is thought to originate in the heart itself and not in the aortic body. There are species differences; in the rabbit there was a direct depressant action on the heart while in the dog central depressant action was proved. In cats, injection of serum or plasma may elicit depressor reflexes originating in the lungs (Brodie effect) and in the left ventricle [Dawes & Feldberg (73)]. Walcott & Deyrup (74) have shown that intravenous injection of small volumes of hypertonic saline or glucose causes initial cardiac irregularities which are followed by transient slowing. Both afferent and efferent components of the reflex arc run in the vagus. It is uncertain if there is any connection between any of the above observations and the bradycardia and arrhythmia produced by the injection of tetanus toxin into the central end of the cut vagus nerve, or even into nearby tissues (75).

According to the electrocardiographic evidence ATP affects the sinoatrial node and conducting system and the myocardium in the guinea pig, cat, and man. The effect on cardiac rhythm varies with the dose; but while small doses in man produced tachycardia, the usual effect was a sinus slowing, prolongation of the P-R interval and the appearance of heart block [Wayne, Goodwin & Stoner (76)]. In the guinea pig the main action of ATP is upon the atrioventricular node whereas in man and the cat it is chiefly upon the sinoatrial node. Part of the effect in the cat and in man is produced by a reflex in which the vagus is the efferent path. In man, if vagal action is prevented by atropine, atrioventricular block is not produced although sinus slowing is still produced. Judging by ectopic beats and depression of the S-T segment ATP may have a direct effect on the myocardium. The results of Emmelin & Feldberg (72), mentioned previously, suggest that the slowing may be caused by (a) direct action on the heart, (b) through a reflex whose receptors are in the heart, or

(c) by direct action on the cardiac inhibitory centre. Madinaveitia & Raventós (77) found that the cardiac effects of adenosine and ATP were reduced by previous administration of quinine, mepacrine, pamaquine, and paludrine.

*Action potentials in cardiac nerves.*—Jarisch & Zotterman (78) have recorded action potentials in small nerve branches running from both atria to the vagus trunk and have correlated them with the electrocardiogram and with the pressure changes in the atria. Two distinct volleys occur in each heart cycle. One follows immediately after the P wave and ends abruptly at QRS; the other commences just before T and ends shortly before P. Alteration of the pressures within the heart modified the impulse pattern. In general, a rise of pressure was followed by increased frequency of impulses and when the caval veins were clamped the second volley disappeared although the atrial volley remained. From the effects produced by stimulating the interior of the atria with a blunt rod, the impulses appear to originate in the orifices of the venae cavae and the pulmonary veins and in the interatrial septum.

Whitteridge (79) worked with single fibres from the cervical vagus and found volleys of action potentials corresponding to the *a*, *c*, and *v* waves of the venous pressure. The impulses are thought to originate in the great veins or in the right atrium and they increase in frequency during a respiratory cycle or when the venous return is increased by abdominal compression. Another group of impulses was recorded during late systole and it is suggested that they come from pulmonary vascular receptors. Some action potentials obtained from the depressor nerve during the isometric contraction phase may arise in the right ventricle or the inter-ventricular septum.

The role of all of these fibres is uncertain. Jarisch & Zotterman (78) found that stimulation of the central ends of the nerves after section never caused acceleration of the heart and there is no evidence that they are concerned with the supposed Bainbridge reflex. But injection of veratrine caused a big increase in the frequency of impulses and therefore it is possible that the fibres are the afferent pathways for the reflexes discussed previously in this section. The effect of veratrine is abolished by the intravenous injection of 20 to 50 mg. of calcium chloride and enhanced by 10 mg. of sodium citrate. The depressor fibres are unaffected by veratrine even in 100  $\mu$ g. doses.

*Effects of exercise and posture on the heart rate.*—Electrocardiograms and intra-arterial blood pressure records have been made by Green, Iglauer & McGuire (80) to show the effect of tilting. Knox (81, 82) has shown that in assessing the results of exercise tolerance tests, allowance should be made for any alterations in posture which of themselves might alter the heart rate. In cases of atrial fibrillation the heart rate increased during a stepping test and the results were repeatable. Digitalization diminished the extent of the rise but did not abolish it. Morse, Schultz & Cassels (83) studied the effects of exhausting exercise on heart rate in boys aged 10 to 17 years. The maximum rate, which averaged 196 beats per min., was independent of the age but it was reached more slowly in the younger boys. Recovery to resting rate was slower in the older boys.

Compared with ventilation volume, cardiac output, and arterial blood pressure, the heart rate returns slowly to the resting level after severe exercise. Herxheimer (84) concluded that this was due to persistent vasodilation in the exercised muscles causing a reduction in effective blood volume. The heart rate recovers more rapidly if the legs, used in the exercise, are lightly bandaged at the beginning of the recovery period.

*Effects of temperature on heart rate.*—Cardiovascular changes induced by exposure to cold have been studied in dogs by Prec *et al.* (85) and in infant rats by Fairfield (86). In dogs in the initial stages there was shivering, increase in cardiac output, and in heart rate. As cooling continued the cardiac output and the heart rate fell. There was prolongation of systole with atrioventricular and ventricular block. Changes in the rat were similar except there were no early compensatory changes and at low thermal temperature the rat reacted as though it were poikilothermic.

When dogs anaesthetized with sodium pentobarbital were exposed to radiant heat sufficient to raise body temperature to 42°C. there was an increase in heart rate and oxygen uptake but cardiac output fell. There was a reduction in circulating blood volume and a diminished venous return according to Prec *et al.* (87). Peripheral vascular collapse sometimes occurred and may be irreversible. Cooper & Kerslake (88) exposed young men to radiant heat and after allowing for an increase in heart rate due to the rise in body temperature claimed that there was a relationship between heart rate and skin temperature.

*Disorders of rhythm and applied pharmacology.*—In view of recent questionings of the arrangement and working of the conducting system in the heart, Kistin (89) has reinvestigated the situation and connections of the atrioventricular node and has failed to find any atrioventricular connections other than those of the Bundle of His.

Smithy (90) found that procaine, if employed to prevent extrasystoles when the heart is being manipulated, is only effective when injected into the myocardium. It is held by Touroff & Adelman (91) that it may also prevent the onset of ventricular fibrillation as a sequel to cardiac arrest.

Oppenheimer *et al.* (92) have shown that single therapeutic doses (4 mg. per kg.) of procaine caused no alteration in the electrocardiogram in the anaesthetized dog, while they and Uhley & Wilburne (93) found that larger doses induced intraventricular block and finally fibrillation. It is probably necessary to distinguish between the actions of procaine on receptors in the heart and on the myocardium. Rosenberg *et al.* (94) found that diethylaminoethanol, a hydrolytic product of procaine, will prevent ventricular tachycardia and premature contractions in dogs under cyclopropane anaesthesia, although it is less active than procaine itself.

The activity and mode of activity of selective blocking agents continue to arouse interest. Nickerson (95) in a comprehensive review deals with the various types of adrenergic blocking agents investigated during the past decade, including their actions on the heart. Although dibenamine (dibenzyl-dichloroethylamine) prevents the arrhythmias induced by epinephrine in the presence of cyclopropane and other hydrocarbons, it is ineffective against the chronotropic and positive inotropic effects of epinephrine on the mammalian heart. A series of  $\beta$ -chloroethyl amines (including dibenamine) tested by Hunt (96) on papillary muscle had no effect on the excitatory response to epinephrine, norepinephrine or isopropyl-norepinephrine. Nickerson & Nomaguchi (97) regard the action of dibenamine in reducing pressor effects as an important factor in preventing arrhythmias.

Moe *et al.* (98) agree that alterations in arterial blood pressure caused by epinephrine in the presence of cyclopropane and other agents may play some part in producing ventricular tachycardia and ventricular fibrillation, but they were unable to block by atropine or tetraethylammonium any reflex pathways involved.

These workers think that dibenamine is effective partly by preventing the pressor response to epinephrine and partly by a direct action on the heart.

Rather by contrast, Youmans, Goodman & Gould (99) have restored normal sinus rhythm in cases of paroxysmal supraventricular tachycardia by intravenous injection of neosynephrine. The pressor response was not important in producing ventricular fibrillation in dogs by epinephrine under barbital anaesthesia during chloroform inhalation, according to Huggins *et al.* (100), but adrenergic blocking agents gave protection. Melville (101) takes a similar view about the pressor response but found that coronary dilator drugs such as ephedrine, amyl nitrite, and nitroglycerine protect effectively against fibrillation even when the pressor effect was maintained by epinephrine.

Bennett, Dhuner & Orth (102) found some dihydroergot compounds effective in preventing cyclopropane-epinephrine induced cardiac irregularities in dogs and monkeys but did not analyze the mode of action. Various aliphatic sympathomimetic amines tested by Murphy & Meek (103) produced tachycardia during cyclopropane anaesthesia. Fastier & Smirk (104) found that amarin (2,4,5-triphenyldihydroiminazole) caused arrhythmia and heart block. Subsequent injection of epinephrine caused ventricular flutter. From a group of hydrocarbons tested by Krantz, Carr & Vitcha (105) ethylene was the only one inhaled which did not lead to ventricular tachycardia and fibrillation after epinephrine injections.

The effects produced by anticholinesterase drugs on the cardiovascular system are reviewed by Koelle & Gilman (106).

#### THE NUTRITION OF THE HEART

*Coronary vessels.*—Wagner & Poindexter (107) described a method of demonstrating the coronary arterial system by injecting nylon. Excellent photographs are given but the method does not seem to show capillary or venous pathways. Among the attempts to find a successful method of revascularizing the heart, methods are described by Beck *et al.* (108) and Roberts (109) for grafting a systemic artery, e.g., internal mammary, into the coronary sinus. Subsequent ligation of a coronary artery did not cause infarction. Boone & Hubbell (110) reported that induced pericardial adhesions do not give a blood supply comparable with the coronary flow

even when they are well vascularized. Manning (111) found that dibenamine did not prevent the onset of ventricular fibrillation after coronary occlusion.

*Regulation of coronary flow.*—Eckstein *et al.* (112) stimulated the left cardiac accelerator nerves in dogs and found an increase in vigour of contraction, cardiac output, oxygen uptake, and coronary flow. If the external work was limited there was still an increase in oxygen uptake and in coronary flow, and cardiac efficiency was reduced. The effects are similar to those classically described for epinephrine on the heart-lung preparation.

Leroy, Nalefski & Christy (113) noticed that adrenergic blocking agents such as tetraethylammonium bromide and dibenamine had no direct effect on coronary flow and, unlike the action on peripheral vessels, did not influence the action of epinephrine. The possibility that ligation of one coronary artery might reflexly cause constriction of others was investigated by Opdyke & Selkurt (114), who found no unequivocal evidence to support the hypothesis. Eckel *et al.* (115) believe that coronary flow is adjusted according to the metabolic activity of the myocardium. But Foltz, Rubin & Steiger (116) found that although aminophylline increased cardiac work and rate of oxygen uptake there was not a proportionate increase in the coronary flow. It is possible that aminophylline acts on the myocardium rather than on the coronary vessels. These findings may explain some of the conflicting reports about the effect of aminophylline on the capacity for effort which are reviewed by Bakst *et al.* (117). Anrep, Kenawy & Barsoum (118) found that khellin (a dimethoxymethylfurano chromone) is a more powerful coronary vasodilator than aminophylline.

Folkow, Frost & Uvnäs (119) demonstrated in perfusion experiments on the dog heart (not beating and often fibrillating) that acetylcholine increased coronary flow. The observations were used to support the hypothesis of Folkow that acetylcholine is the transmitter for sympathetic coronary vasodilator fibres. Epinephrine and, to a smaller extent, norepinephrine, also produced an increase in coronary flow but this was interpreted as a consequence of increased myocardial activity rather than as a direct action on the vessels.

Stein (120) showed that the symptoms induced in man by intravenous injection of ergonovine are characteristic of coronary insufficiency and suggested that the drug might be used to assess

the condition of the coronary circulation. Stewart, Horger & Sorenson (121) and Burchell, Pruitt & Barnes (122) have discussed the value of the anoxaemia test in assessing coronary insufficiency. In dogs breathing 8 to 10 per cent oxygen mixtures the oxygen content of the coronary venous blood was reduced to 2 vols. per cent.

*Metabolism of the heart.*—Direct study of the metabolism of the human heart has been forwarded by catheterisation of the coronary venous system. Aitken & Eaton (123) have collected blood from the middle coronary vein. Bing *et al.* (124) catheterised the coronary sinus and measured coronary flow (by the nitrous oxide method) and the oxygen uptake of the heart. Mean values were: coronary flow, 65 cc. per min. per 100 gm. of ventricular tissue; arteriovenous oxygen difference, 11 vol. per cent; oxygen uptake, 7.8 cc. per 100 gm. per min. Left ventricular work and efficiency were calculated for various conditions. The efficiency was highest in essential hypertension and lowest in cases of cardiac failure. Culbertson, Halperin & Wilkins (125) found a similar arteriovenous difference and also recorded coronary sinus pressures.

Prec. *et al.* (126) have recalculated the external work of the human heart using data from catheterisations and angiocardiology. The kinetic energy is only 1.4 per cent of the total work of both ventricles in a resting subject.

Lactate and pyruvate are regarded by Goodale *et al.* (127) as preferred materials for cardiac metabolism and their usage may account for 20 to 70 per cent of the oxygen uptake. In general, their usage varies with the arterial concentration but when a dog is submitted to stress as by epinephrine infusion, haemorrhage, or shock, the lactate uptake is considerably reduced although there may not be much change in the pyruvate oxidation [Goodale & Hackel (128)]. Braun (129) has attempted to show the influence of niacinamide in the metabolic processes of heart muscle by treating the perfused heart with 3-acetylpyridine as a biological antagonist. Arrhythmias developed which could be abolished by the addition of niacinamide. It is suggested that since there may be a continuous loss of niacinamide from a perfused heart that niacinamide and probably other vitamins should be added to the perfusing fluid. Electrocardiographic changes attributed to vitamin deficiency occurring during convalescence after typhoid fever

were successfully treated with niacin (130). Hackel *et al.* (131) found that pyruvate and lactate utilization fell in acute and chronic thiamine deficiency.

Respiration of dog and guinea pig heart slices is greatly depressed by concentrations of pentobarbital, chlorobutanol, paraldehyde, and propazone, all of which produce a moderate degree of failure in the dog heart-lung preparation. The negative inotropic action of narcotics may not be due to a reduction of oxidative metabolism but, according to Wollenberger (132), to a more direct action on myocardial contractile processes.

*The action of acetylcholine.*—The Oxford school has further investigated the stimulating action of acetylcholine on the myocardium. Vane (133) has shown among other actions, that the beat of the isolated rabbit atrium preparation is stopped by paludrine, or the beat may stop spontaneously about twenty-four hours after the atria have been placed in Tyrode solution. Burn & Vane (134) and Bülbring & Burn (135) discovered that in either of these conditions the beat could be restarted by the addition of acetylcholine to the fluid bath and that further additions increased the rate and amplitude of the contractions. It is not thought that acetylcholine acts by releasing an epinephrine-like substance because this would be a nicotine-like action of acetylcholine and neither nicotine nor benzoylcholine, which is said to have only nicotine-like properties, will start the beat; but Bovet's acetal compound, which is without nicotine-like action will start it. Once the beat is fully established, the more usual inhibitory characteristics of acetylcholine were observed. Acetylcholine synthesis may be an essential part of myocardial metabolism. The acetylcholine-synthesizing power of acetone-dried powder from the fresh, strongly beating atrium is high and that of the stopped atrium is low, but it can be increased in the latter by the addition of small quantities of acetylcholine. In addition to acetylcholine itself, several acetylcholine-like compounds will restart the beat stopped by paludrine according to Vane (136). Callebaut *et al.* (137) found that prolongation of an acute anoxic condition increased the sensitivity of the heart to intra-arterial injection of acetylcholine.

#### ELECTRICAL PHENOMENA

The view that the electrocardiogram can be interpreted by re-

garding the myocardium as a syncytial cell was supported by Churney, Ashman & Byer (138), who obtained electrograms devised from a strip of turtle heart maintained in a fluid conductor. Conduction in the strips was considered as in a single fibre and variations in the rate of repolarization suggested that the tissue was not homogeneous in its electrical properties. Curtis (139) used small bundles of fibres from the turtle heart. The period of depolarization after stimulation corresponded with the period of contraction and the S-T interval. The T-wave represents repolarization. Garb & Chenoweth (140) used a preparation of isolated papillary muscle in a fluid conductor and recorded monophasic waves similar to the R and T waves of the electrocardiogram. The deflection was "T" reversed in anoxic conditions.

Hellerstein & Liebow (141) were able to control the sign of the T wave by inducing a temperature gradient between epicardium and endocardium. When the gradient was towards the endocardium and the electrode intracardiac, T was negative; T was also negative when the electrode was epicardial and the temperature gradient towards the epicardium, or if the endocardium of the opposite wall was cooled. Positive T waves were obtained when the temperature gradient and the position of the electrode were reversed, and it appears that changes in T can be produced by altering the rate and order of the endocardial-epicardial laminar repolarisation.

*Electrocardiograms: definition of electrode position and grouping.*

—The British Cardiac Society (142) has recommended certain leads and combinations for recording electrocardiograms and has suggested appropriate terminology. Amongst other changes, the discontinuance of leads CR and CF is recommended. The recommendations appear to be strengthened by a further experimental analysis of the validity of the Wilson central terminal made by Dolgin, Grau & Katz (143) which seems to establish, for all practical purposes, the claim made for it as an indifferent reference point for unipolar electrocardiography. A mathematical analysis of the same problem made by Rappaport & Williams (144) reached similar conclusions and pointed to the greater reliability of the Wilson terminal than the Goldberger technique. Bryant, Johnston & Wilson (145) found that the potential of the central terminal differed according to the method of connection in about 10 per cent of cases.

Nahum, Chernoff & Kaufman (146) continued their examination of the electrocardiograms derived from unipolar extremity leads in the dog and induced modifications in them by initiating polarization, altering the rate of repolarization, or injuring specific portions of the ventricles. The origin of the precordial electrocardiogram in dogs has been investigated by Nahum & Hoff (147) by stimulating endocardial areas at various positions relative to the chest electrode. The electrocardiogram arises from a balance of e.m.f., proximal and distal to the electrode, and the topography of the regions which interact to produce a precordial electrocardiogram at a particular chest point has been mapped out by observing the effects of local application of heat and cold, local application of 0.1 M KCl, and production of extrasystoles. It is suggested by Nahum & Chernoff (148) that similar concepts can be applied to the human heart.

Turman & Robb (149) found that after almost complete removal of the turtle heart QRST waves can still be recorded from a small area of pulsating intrapericardial vein. There is no support for a hypothesis that a certain wave arises from a specified area.

Groedel & Vorchardt (150) produced extrasystoles from the atria and ventricles by direct stimulation in man during intrathoracic operations. Although they did not take records through a variety of leads, electrograms from the ventricles and electrocardiograms from chest areas perpendicular to the cardiac contact points were very similar. The chest leads were of lower voltage but were not as variable in form as the electrograms.

*Intracardiac electrography in man.*—Electrical potentials have been recorded from the heart cavities by cardiac catheterisation and intracardiac electrodes although there are obvious difficulties in siting the electrode and maintaining its position. Levine *et al.* (151, 152) showed that the recorded atrial complex depends on the position of the electrode. It is predominantly a downward deflection due to the impulse moving away from the electrode when recorded high in the chamber and upright when the electrode is low. A biphasic complex is obtained from intermediate positions. In the right ventricle the situation was usually similar, the R wave being taller from the apical region than elsewhere. In both atrium and ventricle, premature beats and, in the latter, paroxysms of ventricular tachycardia were induced by the electrode touching the endocardium. A monophasic action current of injury was also

produced in the ventricle when the catheter was in contact with the wall; but a corresponding deviation in the RS-T segment was not shown in the limb or chest leads, showing that a small localized injury may produce no effect through the surface leads. When the heart is slowed, as by eliciting the carotid sinus reflex, there is apparent displacement of the pace maker to a lower position in the right atrium. There is little or no shortening of the P-R interval [Levine *et al.* (153)]. Points about methods are described by Kisch *et al.* (154).

Sodi-Pallares *et al.* (155) have confirmed Lewis's hypothesis that the upper left portion is the first part of the interventricular septum to be depolarised and a high right branch bundle block does not affect the early activation of the septum.

*Axis deviation.*—The effect of posture in altering the position of the electrical axis has been interestingly demonstrated by Jones & Feil (156) in human cases of bundle branch block, although the precordial leads were not affected as much as the limb leads. Sturkie (157) showed that alterations in the position of the heart of the chicken caused corresponding alterations in the electrocardiogram and the electrical axis. Reference to orthodiagrams has confirmed that the form of the QRS complex correctly indicates the direction of the anatomical axis in a large majority of healthy human beings (158).

Jones & Feil (159) have examined a number of subjects who subsequently developed branch bundle block. The patients already had abnormal axis deviation which was only changed slightly (mean, 12 per cent) in the same direction when the block occurred. Therefore the types of curve seen in the different types of branch bundle block may be due to the previous electrocardiogram pattern and not to the block.

Methods for assessing the electrical axis, its relationship to the anatomical axis, and the changes produced by alteration in posture and by ventricular hypertrophy are discussed by a large number of other authors.

#### LITERATURE CITED

1. REMINGTON, J. W., HAMILTON, W. F., AND ALQUIST, R. P., *Am. J. Physiol.*, **154**, 6 (1948)
2. SCHLAPP, W., AND WALKER, A. G., *J. Physiol. (London)*, **108**, 458 (1949)
3. COBLENTZ, B., HARVEY, R. M., FERRER, M. I., COURSAUD, A., AND RICHARDS, D. W., *Brit. Heart J.*, **11**, 1 (1949)

4. HELLEMS, H. K., HAYNES, F. W., DEXTER, H., AND KINNEY, T. D., *Am. J. Physiol.*, **155**, 98 (1948)
5. BOONE, B. R., RANDAK, E. F., ELLINGER, G. F., AND OPPENHEIMER, M. J., *J. Applied Physiol.*, **1**, 534 (1949)
6. RAPPAPORT, M., AND SARNOFF, S. J., *Federation Proc.*, **8**, 130 (1949)
7. PRITCHARD, W. H., ECKSTEIN, R. W., ECKEL, R., PARSONS, C. L., AND LOWE, T. E., *Federation Proc.*, **8**, 128 (1949)
8. PETERSON, L. H., DRIPPS, R. D., AND RISMAN, G. C., *Am. Heart J.*, **37**, 771 (1949)
9. TOMPKINS, H. E., *Am. Heart J.*, **37**, 783 (1949)
10. LAGERLOF, H., AND WERKO, L., *Acta Physiol. Scand.*, **16**, 75 (1948)
11. BATTRO, A., BIDOGGIA, H., PIETRAFESA, E. R., AND LABOURT, F. E., *Am. Heart J.*, **37**, 11 (1949)
12. SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L., *Am. J. Physiol.*, **154**, 316 (1948)
13. OPDYKE, D. F., DUOMARCO, G., DILLON, W. H., SCHREIBER, H., LITTLE, R. C. AND SEELY, R. D., *Am. J. Physiol.*, **154**, 258 (1948)
14. OPDYKE, D. F., AND BRECHER, G. A., *Federation Proc.*, **8**, 121 (1949)
15. MARTIN, W. B., AND ESSEX, H. E., *Am. J. Physiol.*, **155**, 453 (1948)
16. LITTLE, R. C., HAWLEY, J. G., AND OPDYKE, D. F., *Federation Proc.*, **8**, 98 (1949)
17. REISS, R. A., AND DIPALMA, J. R., *Am. J. Physiol.*, **155**, 336 (1948)
18. WOLLENBERGER, A., AND KRAYER, O., *J. Pharmacol. Exptl. Therap.*, **94**, 439 (1948)
19. WOODS, L. A., WYNGAARDEN, J. B., RENNICK, B., AND SEEVERS, M. H., *J. Pharmacol. Exptl. Therap.*, **95**, 328 (1949)
20. DILLON, W. H., AND SCHREIBER, H., *Am. J. Physiol.*, **154**, 281 (1948)
21. ROBBARD, S., AND BROWN, F., *Am. J. Physiol.*, **155**, 464 (1948)
22. COURNAND, A., RILEY, R. L., AND HIMMELSTEIN, A., *Federation Proc.*, **8**, 30 (1949)
23. BORDEN, C., WILSON, R. H., AND EBERT, R. V., *J. Lab. Clin. Med.*, **33**, 1543 (1948)
24. GRISWOLD, H. E., BING, R. J., HANDELSMAN, J. C., CAMPBELL, J. A., AND LE BRUN, E., *Bull. Johns Hopkins Hosp.*, **84**, 76 (1949)
25. TAYLOR, B. E., POLLACK, A. A., BURCHELL, H. B., CLAGETT, O. T., AND WOOD, E. H., *Am. J. Physiol.*, **155**, 472 (1948)
26. GROVER, R. F., SWANN, H., AND MAASKE, C. A., *Federation Proc.*, **8**, 63 (1949)
27. WOOD, E. H., TAYLOR, B. E., AND KNUTSON, J., *Federation Proc.*, **8**, 171 (1949)
28. PRINZMETAL, M., CORDAY, E., SPRITZLER, R. G., AND FLIEG, W., *J. Am. Med. Assoc.*, **139**, 617 (1949)
29. DUOMARCO, J. L., DILLON, W. H., AND WIGGERS, C. J., *Am. J. Physiol.*, **154**, 290 (1948)
30. REMINGTON, J. W., AND HAMILTON, J. F., *Am. J. Physiol.*, **148**, 25 (1947)
31. WERKO, L., AND LAGERLOF, H., *Nord. Med.*, **38**, 1163 (1948)
32. WERKO, L., BERSEUS, S., AND LAGERLOF, H., *J. Clin. Invest.*, **28**, 516 (1949)
33. TANNER, J. M., *J. Clin. Invest.*, **28**, 567 (1949)

34. NICKERSON, J. L., *J. Clin. Invest.*, **28**, 369 (1949)
35. MORRISSEY, M. J., AND PALMER, A. J., *Med. J. Australia*, **1**, 113 (1949)
36. RING, G. C., BALABAN, M., AND OPPENHEIMER, M. J., *Am. J. Physiol.*, **157**, 343 (1949)
37. MEIER, R., TRIPOD, J., AND WIRZ, E., *Helv. Physiol. et Pharmacol. Acta*, **7**, 210 (1949)
38. SEELY, R. D., *Am. J. Physiol.*, **154**, 273 (1948)
39. MAY, L. G., BENNETT, A., LANE, A. L., FUTCH, E. D., SCHOOMER, M. L., AND GREGORY, R., *J. Lab. Clin. Med.*, **33**, 1494 (1948)
40. BOLOMEY, A. A., MICHIE, A. J., MICHIE, C., BREED, E. S., SCHREINER, E., AND LAUSON, H. D., *J. Clin. Invest.*, **28**, 10 (1949)
41. RILEY, R. L., HIMMELSTEIN, A., MOTLEY, H. L., WEINER, H. M., AND COURNAND, A., *Am. J. Physiol.*, **152**, 372 (1948)
42. PETERSON, L. H., SCHNABEL, T. D., FITZPATRICK, H., AND BAZETT, H. C., *Am. J. Physiol.*, **155**, 460 (1948)
43. COHEN, S. M., EDHOLM, O. G., HOWARTH, S., MCMICHAEL, J., AND SHARPEY-SCHAFER, E. P., *Clin. Sci.*, **7**, 35 (1948)
44. BAKER, C., AND TROUNCE, J. R., *Brit. Heart J.*, **11**, 109 (1949)
45. STOTZ, W., *Z. Kreislaufforsch.*, **37**, 302 (1948)
46. FELDMAN, M., RODBARD, S., AND KATZ, L. N., *Am. J. Physiol.*, **154**, 391 (1948)
47. IRWIN, H. R., AND WINSOR, T., *J. Pediat.*, **33**, 556 (1948)
48. POLLACK, A. A., TAYLOR, B. E., AND MYERS, T. T., *J. Clin. Invest.*, **28**, 559 (1949)
49. SHAW, R. S., HENRY, J. P., GAMBLE, J. L., AND GAUER, O., *J. Applied Physiol.*, **1**, 441 (1948)
50. BRITTON, S. W., *Am. J. Physiol.*, **156**, 1 (1949)
51. WOOD, P., AND PAULETT, J., *Brit. Heart J.*, **11**, 83 (1949)
52. MARESCH, M. M., *Pediatrics*, **2**, 382 (1948)
53. LINZBACH, A. J., *Klin. Wochschr.*, **26**, 459 (1948)
54. LOWE, T. E., AND BATE, E. W., *Med. J. Australia*, **1**, 467 (1948)
55. WALLS, E. W., *Brit. Heart J.*, **10**, 188 (1948)
56. DOTTER, C. T., AND STEINBERG, I., *J. Am. Med. Assoc.*, **139**, 566 (1949)
57. BROCKLEBANK, J. A., *Brit. J. Radiology*, **21**, 393 (1948)
58. KEELE, K. D., *Brit. J. Radiology*, **21**, 380 (1948)
59. CARSON, M. J., BURFORD, T. H., SCOTT, W. G., AND GOODFRIEND, J., *J. Pediat.*, **33**, 525 (1948)
60. BURFORD, T. H., AND CARSON, M. J., *J. Pediat.*, **33**, 675 (1948)
61. SUTTON, G. C., WENDEL, G. E., AND GRANT, H. E., *J. Lab. Clin. Med.*, **33**, 1502 (1948)
62. HAMILTON, W. F., AND DOW, P., *Federation Proc.*, **8**, 66 (1949)
63. KAY, C. F., WOODS, J. W., JR., ZINSSER, H., AND BENJAMIN, J. M., JR., *J. Clin. Invest.*, **28**, 228 (1949)
64. CHAPMAN, E. M., KINSEY, D., CHAPMAN, W. P., AND SMITHWICK, R. H., *J. Am. Med. Assoc.*, **137**, 579 (1948)
65. FOLKOW, B., FROST, J., HAEGER, K., AND UVNAS, B., *Acta Physiol. Scand.*, **15**, 4, 421 (1948)

66. GOLDENBERG, M., PINES, K. L., BALDWIN, E. DE F., GREENE, D. G., AND ROTH, C. E., *Am. J. Med.*, **5**, 792 (1948)
67. DUNCANSON, D., STEWART, T., AND EDHOLM, O. G., *Federation Proc.*, **8**, 37 (1949)
68. BARCROFT, H., AND KONZETT, H., *Lancet*, **I**, 147 (1949)
69. CONSTANT, G., ANDRONIS, A., AND OGDEN, E., *Federation Proc.*, **8**, 27 (1949)
70. FREIS, E. D., STANTON, J. R., CULBERTSON, J. W., LITTER, J., HALPERIN, M. H., BURNETT, C. H., AND WILKINS, R. W., *J. Clin. Invest.*, **28**, 353 (1949)
71. AVIADO, D. M., AND PONTIUS, R. G., *Federation Proc.*, **8**, 5 (1949)
72. EMMELIN, N., AND FELDBERG, W., *Brit. J. Pharmacol.*, **3**, 273 (1948)
73. DAWES, G. S., AND FELDBERG, W., *J. Physiol. (London)*, **108**, 362 (1949)
74. WALCOTT, W. W., AND DEYRUP, I. J., *Am. J. Physiol.*, **154**, 328, 336 (1948)
75. AMBACHE, H., AND LIPPOLD, O. C. J., *J. Physiol. (London)*, **108**, 186 (1949)
76. WAYNE, E. J., GOODWIN, J. F., AND STONER, H. B., *Brit. Heart J.*, **11**, 55 (1949)
77. MADINAVEITIA, J., AND RAVENTÓS, J., *Brit. J. Pharmacol.*, **4**, 81 (1949)
78. JARISCH, A., AND ZOTTERMAN, Y., *Acta Physiol. Scand.*, **15**, 31 (1948)
79. WHITTERIDGE, D., *J. Physiol. (London)*, **107**, 496 (1948)
80. GREEN, R. S., IGLAUER, A., AND MCGUIRE, J., *J. Lab. Clin. Med.*, **33**, 951 (1948)
81. KNOX, J. A. C., *J. Physiol. (London)*, **108**, 340 (1949)
82. KNOX, J. A. C., *Brit. Heart J.*, **11**, 119 (1949)
83. MORSE, M., SCHLUTZ, F. W., AND CASSELS, D. E., *J. Applied Physiol.*, **1**, 683 (1949)
84. HERKHEIMER, H., *J. Applied Physiol.*, **1**, 279 (1948)
85. PREC, O., ROSENMAN, R., BRAUN, K., HARRIS, R., RODBARD, S., AND KATZ, L. N., *J. Clin. Invest.*, **28**, 293 (1949)
86. FAIRFIELD, J., *Am. J. Physiol.*, **155**, 355 (1948)
87. PREC, O., ROSENMAN, R., BRAUN, K., HARRIS, R., RODBARD, S., AND KATZ, L. N., *J. Clin. Invest.*, **28**, 301 (1949)
88. COOPER, K. E., AND KERSLAKE, D. M., *J. Physiol. (London)*, **107**, 42 (1948)
89. KISTIN, A. D., *Am. Heart J.*, **37**, 849 (1949)
90. SMITHY, H. G., *Southern Surgeon*, **14**, 611 (1948)
91. TOUROFF, A. S. W., AND ADELMAN, M. H., *J. Am. Med. Assoc.*, **139**, 844 (1949)
92. OPPENHEIMER, M. J., LONG, J. H., WESTER, W. R., AND DURANT, T. M., *Am. J. Physiol.*, **155**, 457 (1948)
93. UHLEY, M. H., AND WILBURNE, M., *Am. Heart J.*, **36**, 576 (1948)
94. ROSENBERG, B., KAYDEN, H. J., LIEF, P. A., MARK, L. C., STEELE, J. M., AND BRODIE, B. B., *J. Pharmacol. Exptl. Therap.*, **95**, 18 (1949)
95. NICKERSON, M., *J. Pharmacol. Exptl. Therap.*, **95**, 27 (1949)
96. HUNT, C. C., *J. Pharmacol. Exptl. Therap.*, **95**, 177 (1949)
97. NICKERSON, M., AND NOMAGUCHI, G. M., *J. Pharmacol. Exptl. Therap.*, **95**, 1 (1949)
98. MOE, G. K., MALTON, D., RENNICK, R., AND FREYBURGER, W. A., *J. Pharmacol. Exptl. Therap.*, **94**, 319 (1948)

99. YOUMANS, W. B., GOODMAN, M. J., AND GOULD, J., *Am. Heart J.*, **37**, 359 (1949)
100. HUGGINS, R. A., MORSE, R. A., HANDLEY, C. A., AND LA FORGE, M., *J. Pharmacol. Exptl. Therap.*, **95**, 312 (1949)
101. MELVILLE, K. I., *J. Pharmacol. Exptl. Therap.*, **94**, 136 (1948)
102. BENNETT, W. D., DHUNER, K. G., AND ORTH, O. S., *J. Pharmacol. Exptl. Therap.*, **95**, 287 (1949)
103. MURPHY, Q. R., AND MEEK, W. J., *Federation Proc.*, **8**, 116 (1949)
104. FASTIER, F. N., AND SMIRK, F. H., *J. Physiol. (London)*, **107**, 318 (1948)
105. KRANTZ, J. C., CARR, C. J., AND VITCHA, J. F., *J. Pharmacol. Exptl. Therap.*, **94**, 315 (1948)
106. KOELLE, G. B., AND GILMAN, A., *J. Pharmacol. Exptl. Therap.*, **95**, 166 (1949)
107. WAGNER, A., AND POINDEXTER, C. A., *Am. Heart J.*, **37**, 258 (1949)
108. BECK, C. S., STANTON, W., BATIUCHOCK, W., AND LEITER, E., *J. Am. Med. Assoc.*, **137**, 436 (1948)
109. ROBERTS, J. T., *Federation Proc.*, **8**, 176 (1949)
110. BOONE, A. W., AND HUBBELL, D. S., *Surg. Gynecol. Obstet.*, **87**, 9 (1948)
111. MANNING, G. W., *Federation Proc.*, **8**, 105 (1949)
112. ECKSTEIN, R. W., STROUD, M., DOWLING, C. V., ECKEL, R., AND PRITCHARD, W. H., *Federation Proc.*, **8**, 38 (1949)
113. LEROY, G. V., NALEFSKI, L. A., AND CHRISTY, H. W., *J. Lab. Clin. Med.*, **33**, 1496 (1948)
114. OPDYKE, D. F., AND SELKURT, E. E., *Am. Heart J.*, **36**, 73 (1948)
115. ECKEL, R., ECKSTEIN, R. W., STROUD, M., AND PRITCHARD, W. H., *Federation Proc.*, **8**, 38 (1949)
116. FOLTZ, E. L., RUBIN, A. J., AND STEIGER, W. A., *Federation Proc.*, **8**, 48 (1949)
117. BAKST, H., KISSIN, M., LEIBOWITZ, S., AND RINZLER, S., *Am. Heart J.*, **36**, 527 (1948)
118. ANREP, G. V., KENAWY, M. R., AND BARSOUM, G. S., *Am. Heart J.*, **37**, 531 (1949)
119. FOLKOW, B., FROST, J., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 201 (1949)
120. STEIN, I., *Am. Heart J.*, **37**, 36 (1949)
121. STEWART, H. J., HORGER, E. L., AND SORENSON, C., *Am. Heart J.*, **36**, 161 (1948)
122. BURCHELL, H. B., PRUITT, R. D., AND BARNES, A. R., *Am. Heart J.*, **36**, 373 (1948)
123. AITKEN, C. J., AND EATON, J. C., *J. Physiol. (London)*, **108**, 17 (1949)
124. BING, R. J., HAMMOND, M., HANDELSMAN, J. C., POWERS, S., AND SPENCER, F., *Bull. Johns Hopkins Hosp.*, **84**, 396 (1949); *Federation Proc.*, **8**, 11 (1949)
125. CULBERTSON, J. W., HALPERIN, M. H., AND WILKINS, R. W., *Am. Heart J.*, **37**, 942 (1949)
126. PREC, O., KATZ, L. N., ROSENMAN, R., AND SENNETT, L. W., *Federation Proc.*, **8**, 128 (1949)
127. GOODALE, W. T., HACKEL, D. B., LUBIN, M., AND WILSON, P. P., *Am. J. Physiol.*, **155**, 439 (1948)
128. GOODALE, W. T., AND HACKEL, D. B., *Federation Proc.*, **8**, 58 (1949)
129. BRAUN, K., *J. Pharmacol. Exptl. Therap.*, **95**, 58 (1949)

130. RACHMILEWITZ, M., AND BRAUN, K., *Am. Heart J.*, **36**, 284 (1948)
131. HACKEL, D. B., GOODALE, W. T., AND JOHNSON, R. P., *Federation Proc.*, **8**, 65 (1949)
132. WOLLENBERGER, A., *J. Pharmacol. Exptl. Therap.*, **94**, 444 (1948)
133. VANE, J. R., *Brit. J. Pharmacol.*, **4**, 14 (1949)
134. BURN, J. H., AND VANE, J. R., *J. Physiol. (London)*, **108**, 104 (1949)
135. BÜLBRING, E., AND BURN, J. H., *J. Physiol. (London)*, **108**, 508 (1949)
136. VANE, J. R., *Brit. J. Pharmacol.*, **3**, 341 (1948)
137. CALLEBAUT, C., FELDMAN, M., ROBBARD, S., AND KATZ, L. N., *J. Lab. Clin. Med.*, **33**, 1495 (1948)
138. CHURNEY, L., ASHMAN, R., AND BYER, E., *Am. J. Physiol.*, **154**, 241 (1948)
139. CURTIS, H. J., *Federation Proc.*, **8**, 30 (1949)
140. GARB, S., AND CHENOWETH, M. B., *Am. J. Physiol.*, **156**, 27 (1949)
141. HELLERSTEIN, H. K., AND LIEBOW, I. M., *J. Lab. Clin. Med.*, **33**, 1498 (1948)
142. COMMITTEE OF THE BRIT. CARDIAC SOC., *Brit. Heart J.*, **11**, 103 (1949)
143. DOLGIN, M., GRAU, S., AND KATZ, L. N., *Am. Heart J.*, **37**, 868 (1949)
144. RAPPAFORT, M. B., AND WILLIAMS, C., *Am. Heart J.*, **37**, 892 (1949)
145. BRYANT, J. M., JOHNSTON, F. D., AND WILSON, F. N., *Am. Heart J.*, **37**, 321 (1949)
146. NAHUM, L. H., CHERNOFF, H. M., AND KAUFMAN, W., *Am. J. Physiol.*, **154**, 369 (1948)
147. NAHUM, L. H., AND HOFF, H. E., *Am. J. Physiol.*, **155**, 215 (1948)
148. NAHUM, L. N., AND CHERNOFF, H. M., *Federation Proc.*, **8**, 117 (1949)
149. TURMAN, W. G., AND ROBB, J. S., *Federation Proc.*, **8**, 167 (1949)
150. GROEDEL, F. M., AND VORCHARDT, P. R., *Exptl. Med. Surg.*, **6**, 213, 225, 246, 280 (1948)
151. LEVINE, H. D., HELLEMS, H. K., WITTENBORG, M. H., AND DEXTER, L., *Am. Heart J.*, **37**, 46 (1949)
152. LEVINE, H. D., HELLEMS, H. K., DEXTER, L., AND TUCKER, A. S., *Am. Heart J.*, **37**, 64 (1949)
153. LEVINE, H. D., HELLEMS, H. K., DOW, J. W., AND GOWDEY, J. F., *Am. J. Physiol.*, **156**, 19 (1949)
154. KISCH, B., SCHWARTZ, B. M., KING, F. H., BRAHMS, S., AND SUSSMAN, M. L., *J. Mt. Sinai Hosp. N. Y.*, **15**, 257 (1948)
155. SODI-PALLARES, D., THOMSEN, P., AND SOBERON, J., *Am. Heart J.*, **36**, 1 (1948)
156. JONES, A., AND FEIL, H., *Am. Heart J.*, **36**, 739 (1948)
157. STURKIE, P. D., *Am. J. Physiol.*, **154**, 251 (1948)
158. HYMAN, A., FAILLEY, R. B., AND ASHMAN, R., *Am. Heart J.*, **36**, 906 (1948)
159. JONES, A. M., AND FEIL, H., *Am. Heart J.*, **36**, 98 (1948)

## KIDNEY<sup>1</sup>

BY J. TRUETA

*Nuffield Professor of Orthopaedic Surgery, Oxford University,  
Oxford, England*

### FUNCTION AND STRUCTURE OF THE KIDNEY IN EARLY LIFE

On a basis of surface area, inulin clearances of premature infants are low compared with those of adults. Urea clearances of premature infants are also low, but cannot be used in estimating glomerular filtration since they have a variable relationship to inulin clearances. Dehydration produced by withholding fluids does not diminish glomerular filtration, but results in increased reabsorption (1). Investigation of renal clearances in premature infants by inulin, urea, mannitol, and *p*-aminohippurate (PAH) ratios has shown that the inulin clearances were not lower after mannitol in half the number whose control inulin clearances were measured prior to the infusion of mannitol. PAH clearances with plasma levels less than 2.0 mg. per 100 ml. and PAH tubular maxima with levels greater than 50 mg. per 100 ml. were measured in four out of ten infants who were less than 14 days old. The average PAH clearances and tubular maxima were 13.2 ml. per min. and 0.97 mg. per min. respectively (2). It has been suggested that there is a direct relationship between the size of the fetuses and infants and the cessation of formation of new glomerular elements, but recent information supports the view that there is an increase in the kidney function related to postnatal age. However, the magnitude of the increase observed in older infants may be less than would be expected in larger infants. Mean values for inulin and PAH clearances and PAH tubular maxima, corrected for surface area in premature infants, ranged from 17 per cent to 58 per cent of normal values. Greater postnatal age appears to increase the rate of development of kidney function in premature infants weighing between 2,100 and 2,500 gm. (3). Another group of investigators has found that when corrected for surface area, the mean value for filtration rate is reduced by 10 to 20 weeks below the value characteristic of adults. Similarly the effective renal blood flow and maximal excretory capacity are reduced by

<sup>1</sup> This review covers in the main the period from January to December 1948.

30 weeks. They develop at different rates during the first three months. In early infancy, there may be disproportionate glomerular surface as well as a functional imbalance, possibly related to increased glomerular pressure, between glomeruli and tubules acting in favor of the former (4). Observations based on patients with healthy kidneys showed that children are able to concentrate from specific gravity 1.020 to 1.037, these figures representing higher values than in adults, and also that there is a gradual fall in the concentration power with increasing age (5).

The development of the renal glomeruli has been followed in histological preparations of post-mortem material from fetuses and full term infants. The visceral layer of the epithelium is columnar in newly differentiated glomeruli and gradually passes through a cuboidal to a squamous form. It begins in the medullary layer of glomeruli and progresses towards the cortex, to reach completion within a few months after birth (6).

#### RENAL CLEARANCES

*Contributions to the study of glomerular and tubular work in normal and pathological human kidneys.*—The use of inulin or creatinine in clearance tests has been criticised. A new agent, tritacin, has been found useful for the purpose. It is a fructose yielding polysaccharide of low molecular weight, 23 per cent soluble in water. It may be injected quickly, causes no shock, and is excreted in 4 hr., none being held up by the tissues. The normal and abnormal clearance values are about the same as with inulin (7). It has been found that in four out of fourteen cases (three healthy and one pathological) the diodrast load necessary to cause a maximal tubular excretion was much higher than in the ten other cases. This is believed to indicate that in these cases the plasma is not evenly supplied to the tubular cells. If some of the cells in these subjects were supplied by a scanty amount of blood compared with the others, the result would be that the diodrast concentration necessary to keep all the tubular cells fully occupied would increase and the "saturation load" would be great compared with the tubular mass (8). The diodrast clearances in some pathological cases indicate that the amount of iodine excreted by the tubules could not be estimated, since the quantity found in the urine was less than the quantity that could be calculated to have been filtered in the glomeruli. A possible explanation offered by

the author is that the sudden considerable increase of the diodrast concentration causes a spasm of the efferent blood vessels. There must have been practically no tubular diodrast excretion at all during the first half hour after the injection in these pathological cases. The author found it difficult to regard the "tubular mass" in pathological cases as an exact measure of the amount of tubular tissue or even as a measure of the number of "excretory units" of the kidney in patients with severely damaged kidneys (9). In a series of experiments on healthy human subjects, it was found that the induction of acidosis by the ingestion of ammonium chloride and the promotion of buffer excretion by the infusion of phosphate or creatinine greatly increased the rate of excretion of titratable acid. Simultaneous measurements of the rate of filtration, reabsorption, and excretion of mono- and dibasic phosphate and carbonic acid demonstrated that the quantity of acid excreted far exceeded that which entered the urine in the glomerular filtrate. Therefore, acid must have been added to the filtrate as it passed along the nephron by some mechanism of active transport resident in the renal tubular cells. It is suggested that this addition of acid is effected by the exchange of hydrogen ions, formed within the tubular cells, for ions of fixed base in the tubular urine. Carbonic acid is the intracellular source of hydrogen ions (10). It was observed when investigating salyrgan and renal tubular secretion of *p*-aminohippurate in the dog and man, that the renal tubular capacity to transfer PAH in man is markedly depressed by salyrgan, whereas in the dog it is unaffected. This indicates a fundamental difference in the transfer mechanism. The data reported re-emphasizes the need for caution in applying information concerning tubular transport mechanism from one species to another (11).

*Renal excretion of potassium.*—The possibility of tubular secretion of potassium has been suggested by isolated observations. In recent studies of electrolyte excretion associated with urea diuresis, potassium clearance increased from 5 to 10 per cent of the creatinine clearance at normal rates of urine flow to 80 to 90 per cent of the creatinine clearance during marked diuresis. This is interpreted as evidence that all of the potassium excreted in the urine cannot be accounted for by the filtration reabsorption theory, but that tubular secretion of potassium also occurs (12). This view is also supported by recent work in normal dogs. A constant rate of

potassium excretion, dissociated from filtered load, occurring after salyrgan administration, suggested a tubular secretory mechanism located, presumably, in the distal tubule. The presence of such a mechanism is suggested by the results of the intravenous administration of potassium chloride solution which yielded rates of potassium excretion considerably above the rates of filtration of potassium at the glomeruli (13). From investigations into the renal excretion of sodium and potassium in rats, data have been accumulated during normal water diuresis which demonstrated that the amount of potassium reabsorbed was closely correlated with the amount of potassium filtered. This correlation persisted when the amount of potassium filtered was raised by increasing the level of potassium in the plasma or by increasing the glomerular filtration rate. The mechanism of renal potassium excretion in rats stands thus in complete contrast to the mechanism of renal excretion of other ions such as chloride and sodium (14).

*Indirect evidence of segmental tubular work.*—It is believed by Oliver (185,186) and his school that roughly 85 percent of the sodium and water in the glomerular filtrate are reabsorbed by the proximal tubule and thin limb of the mammalian kidney, and that tubular urine is isosmotic with plasma half way down the proximal tubule. Work now published appears to suggest, firstly, that the proximal reabsorption of sodium and water are practically independent processes, and, secondly, that proximal water reabsorption is a process of passive diffusion initiated by the active reabsorption of sodium. Passive osmotic equilibration may be completed in the thin limb so that the urine delivery to the distal tubule is normally isosmotic with plasma. Tentative evidence is adduced that under the action of antidiuretic hormone (ADH), distal reabsorption of water reaches a maximal rate  $T_m^d_{H_2O}$  and that under conditions conducive to stability, the distal reabsorption of sodium is also limited by a maximal rate  $T_m^d_{NA}$ . Under such circumstances, sodium excretion is conditioned by the filtration rate as well as the plasma level of sodium (15). A decrease in the diodrast clearance has been caused by injection of uranyl acetate into rabbits and dogs with no immediate diminution in chloride reabsorption although there was diminution in diodrast secretion. These findings suggest that the uranyl salts interfered with the function of the proximal convolution of the nephron. The secretion of diodrast was affected more markedly than the

reabsorption of chloride and the maximal effect on diodrast secretion occurred earlier and persisted longer than the effect on chloride reabsorption. This temporary difference between the minima in chloride reabsorption and diodrast secretion may mean that these two processes occur by different mechanisms in the tubule (16). No satisfactory answer to this most important question seems within reach until our knowledge of the blood supply of each particular segment of the tubules is improved. The problem of alteration in the local renal hemodynamics is, as results obtained with renal clearances have repeatedly stressed, a source of inconsistency. The PAH clearances in rats appear to be different in the experiments with "undisturbed" (slight anaesthesia) and in the "tailcutting" experiments. A difference of 14 per cent was noted, presumably due to an alteration in the renal plasma flow. These differences in renal plasma flow between the methods mentioned above must be the result of an alteration in the local renal hemodynamics which is not associated with a change in the general blood volume. However, the degree to which renal plasma flow is diminished, 14 per cent as indicated by the PAH clearances, is not adequate to explain the 34 per cent fall in creatinine and urea clearances. The author supposes that reabsorption of water, along with the other components of renal function, is affected by the changes in both plasma flow and filtration pressure. Again, we must wait until the differences between the blood supply of the several segments of the tubules are known before an answer to this problem can be given (17). Studies of the renal circulation by a group of workers in Oxford, published last year, does not throw complete light on the fine changes of the two types of circulatory arrangements, cortical and medullary (18). If, as they and others have suggested (19, 20), reabsorption takes place mainly in the medullary region, any change of the medullary circulation may influence reabsorption. The same could be said of changes of the circulation in other segments of the tubules.

*Effects of exercise on the renal circulation.*—The above views seem to be further supported by the numerous contributions on the effects of exercise upon the renal circulation. Barclay *et al.* (21) found in man that with exercise there is depression of the glomerular filtration rate and filtration fraction, as well as of plasma flow. More recent work has shown that during the first 16 min. of walking on a motor-driven treadmill, the renal plasma

flow was decreased in all instances. With light exercise, about 150 ml. of whole blood per min. is diverted from the kidney for circulation elsewhere. For the heaviest work load, the corresponding figure is about 330 ml. Return of the renal plasma flow to basal levels was incomplete after 40 min. of recovery following this exercise. The mechanism which acts to depress renal plasma flow in exercise is uncertain, and this work throws no new light on it. The chief significance of the diversion of blood from the kidney during exercise may be that more blood is made available for working muscles (22). Other work has shown no consistent changes in filtration fractions during and after exercise. Renal vascular resistance increased in normal subjects at least fivefold (taking mean arterial pressure during exercise as normal) during exercise and was still somewhat above normal an hour later. All urines were protein-free before and during heavy exercise, but urines formed during first and second postexercise periods contained protein, which had disappeared by the third 20 min. postexercise collection. This supports, but does not prove, the view that during heavy exercise many glomeruli may have no blood flow (23). Renal vasoconstriction remains light in moderate exercise and is apparently due to nerve impulses, the constricting action of epinephrine on the renal vessels being added as exercise becomes more severe. The renal vasoconstriction which occurs with maximum exercise for relatively brief periods may progress to the point where many glomeruli cease to function as indicated by post-exercise proteinuria (24). These authors suggest that the changes of intrarenal blood distribution described by Trueta *et al.* (18) might possibly explain why, during exercise, the PAH plasma clearance is no longer a measure of renal plasma flow because of shunting of blood through regions which do not extract PAH. Other studies in normal human subjects have shown similar results (25).

*Renal function in cardiac subjects.*—Patients with heart failure who exhibit edema at rest usually have a low resting cardiac output and a correspondingly low resting renal plasma flow with a filtration rate below 70 to 80 ml. per min. Since tubular reabsorption is almost complete, the low filtration of salt and water results in retention of these substances and ultimately edema. Cardiac subjects who show edema only on exercise usually have filtration rates above 70 ml. per min. These subjects fall well below the "critical" level of 70 ml. per min. with exercise. None of the con-

trol subjects had a comparable change in filtration rate, though a few had a definite fall in renal plasma flow. Plasma flow is thus reduced when the cardiac output is insufficient for tissue demands, and tissues such as the brain are better supplied with blood. The metabolic needs of such organs are greater than those of the kidney in proportion to blood supply (26). These authors do not suggest by which mechanism reabsorption is increased in these cases. Other workers have also studied the homeostatic mechanism of diverting blood from the kidney when the cardiac output falls. Further work has shown that in heart failure, the kidney may take, instead of the normal 18 per cent of the total cardiac output, only 7.4 per cent or about two-fifths of normal. Plasma flow and glomerular filtration were measured by aminohippurate and mannitol clearances and, under the conditions of these experiments, the renal tubules reabsorbed a mean value of 13.3 mm. of sodium from every 100 ml. of glomerular filtrate. In patients with congestive heart failure and in normals, physiologically induced variations in the glomerular filtration rate reveal constancy in the sodium reabsorptive mechanism. The decreased excretion rate of sodium in congestive heart failure is attributable to a decreased filtration rate in the presence of normal tubular reabsorption. Despite the variations in renal vasomotor activity and interstitial pressure in this condition, it has been shown by renal vein catheterization that the extraction ratio of *p*-aminohippurate is within normal limits (27).

In studies of the effect that anxiety has on the circulation, it has been found that cardiac output, heart rate, and oxygen consumption are increased. There is a moderate elevation of blood pressure, but the peripheral resistance is decreased. The cardiac output is abnormally high in proportion to the rate of oxygen consumption. When persons with this reaction undertake muscular exercise, the normal relation between cardiac output and rate of oxygen consumption is re-established. In a small group of subjects, anxiety resulted in an increase in peripheral resistance and an elevation of blood pressure, with no change at all in cardiac output. The nature and location of the vascular channel through which the excess quantity of blood circulates in those persons who develop a hyperactive circulation in response to anxiety is a problem of considerable interest. The disproportion of cardiac output to oxygen consumption and the high oxygen content of

mixed venous blood suggests that a considerable proportion of the output is shunted through arteriovenous connections or preferential channels, thus by-passing the capillaries. These authors do not find evidence to indicate the organs in which such shunts are occurring (28). The part played by the kidneys in shunting the blood through arteriovenous vascular channels is not mentioned by these workers. The fact that in shock there is an increase in oxygen content only in the renal venous blood, and not in the blood of the veins of other organs, would make an investigation of this subject worth while (44).

*Changes in renal function effected by external agents.*—The effects of the cold pressor test, in which the foot is immersed in ice water at 1°C. for 15 min., on filtration and effective renal plasma flow have been determined in normal subjects and found to be decreased in six out of seven cases studied, either during or approximately 20 min. thereafter. The average decreases in glomerular filtration rate and effective renal plasma flow, as compared with the control values, were 14 per cent and 21 per cent respectively (29).

The effect of increased intra-abdominal pressure on the renal function of dogs has been investigated and found to be not dissimilar to that determined for man (30). Bradley *et al.* (31) have shown that the renal blood flow, glomerular filtration rate, and maximal rates of glucose reabsorption and diodrast excretion are greatly reduced in man by increased intra-abdominal pressure. These effects may be attributed to simultaneous elevations in renal venous pressure and intrapelvic pressure, which would act respectively to decrease blood flow and to halt urine flow from nephrons which have relatively low terminal intraluminal pressures. Thus a large proportion of the renal parenchyma apparently no longer functions in producing urine. Renal oxygen consumption was determined under these conditions before, during, and following compression of the abdomen by a pneumatic girdle inflated to 80 mm. Hg. The consumption of oxygen by the kidneys averaged 10.3 ml. per min. in the control resting state. With compression it fell to 6.1 ml. per min., a reduction of 41 per cent. At the same time the renal blood flow was reduced on an average by 52 per cent. The urine flow decreased sharply, and the urinary concentration of PAH rose. These authors think that it is interesting that

reduced oxygen consumption during abdominal compression is associated with apparent cessation of urine formation in a certain proportion of nephrons. The possibility that renal oxygen consumption depends upon the relative proportion of tubular tissue actively functioning in the formation of urine from glomerular filtrate cannot be excluded as an explanation of the data presented here. It is not suggested that a relative exclusion of a variable part of the cortex by the intrarenal blood could also explain the decreased oxygen consumption when urine formation ceases (31).

Experiments on renal hyperemia in dogs by intravenous infusion of adenylic acid, adenosine, and adenosinetriphosphate (32), and with the oral administration of cinchone alkaloids (33) have been reported. The role played by hypotension in reducing filtration rate by means of infusion of tissue metabolites is emphasized. In the postinfusion phase, with the blood pressure near control values, the renal plasma flow ranged from 111 to 240 per cent of the controls. It seems worth noticing that the maximal renal hyperemia occurs when the general vasodilator effect of the tissue metabolites has passed off, as judged by the return of blood pressure to normal values. With quinidine and cinchonine, no marked change in the mean arterial blood pressure was recorded; but renal hyperemia was, nevertheless, evident.

#### SHOCK AND RENAL VASCULAR SPASM

There are a series of reports by Overman & Wang (34, 35, 36) on the contributory role of an afferent nervous factor in experimental traumatic shock in the dog. Animals with haemorrhage survived, whereas animals under similar conditions of haemorrhage plus stimulation of the sciatic nerve died. The data provided indicates that afferent impulses excite reflexly the sympathetic nervous system and exert a detrimental effect on the traumatized animals by a further reduction of the tissue blood flow, this being the result of increased vasoconstriction and apparent increased blood viscosity. In the view of these authors, it may appear paradoxical that increased blood pressure following sciatic stimulation exerts a deleterious effect upon the condition of the bleeding animal. Indeed, in their experience, the animals that give the most marked sciatic pressor responses are those that show an early depression of the central nervous system and death (36). Renal

vasoconstriction may, in the view of these workers, contribute to the general vasoconstriction by means of one or more chemical factors from the kidney in ischaemic conditions.

That vasoconstriction seems to increase the severity of shock in dogs is suggested by a series of experiments. Recovery after haemorrhagic shock was greatly accelerated by previous treatment with dibenamine hydrochloride, which prevented extreme vasoconstriction (37). Similar results were obtained in guinea pigs by preventing the intense vasoconstriction of anoxemia by means of intraperitoneal injection of 2.5 mg. per kg. body weight of acetylcholine hydrochloride (38). This had also been the experience of Kalk & Brühl in man (39). Franklin has shown that anoxemia caused intense blanching of the surface of the kidney in rabbits and cats (40). In the goat, severe third degree flame burns caused a marked decrease of effective plasma flow. In one group of experiments, there was an initial sharp decrease in the filtration rate and reabsorptive capacity, followed by a return to normal values (41). Moon gives a review of the renal changes in shock and thinks that the parenchymatous effects of shock may be ascribed in part to the injurious agent itself and, in part, to anoxia. The severe effects, seen regularly in the renal tubules, are probably related to the anuria and other evidence of renal functional deficiency which accompanies shock (42). Sanderson, studying renal failure following abdominal surgical "catastrophe" and alkalosis in man, concludes that the kidney in gravely ill abdominal cases is affected more or less intensely by vasoconstriction. He thinks that his observations would be compatible with diversion of blood from cortex to medulla of the kidney (43).

A comprehensive review of the effects of shock on the kidney was carried out by Van Slyke. He places emphasis on the first or ischemic, phase of shock kidney, and he suspects renal vasoconstriction to be the cause of anuria in this condition. He concurs that the vascular blood is diverted to supply the brain; the necessity for the inclusion of the kidney in the constriction is obvious from the fact that the kidneys in the resting subject normally utilise about 20 per cent of the blood. He considers the possibility that the cortical shunt described by Trueta *et al.* (18) is operating under these conditions, but he attributes to these authors the finding of an increased total blood flow through the kidney when the cortex is excluded, which would be contrary to

his observations in shock. In fact, the reduction in total blood flow, when the renal cortex is totally or partially excluded, is postulated also by Trueta *et al.*, and both Van Slyke and the Oxford workers arrived at this conclusion concurrently (44). In 12 cases of delayed death after shock, complete necrosis of the proximal convoluted tubular epithelium with less degeneration of the distal tubules has been found (45). This is contrary to the findings of Lucké (46).

*Renal anoxia.*—The early work of Barcroft & Brodie (47) on renal function and oxygen consumption has been repeatedly taken up under varying experimental conditions. Adolph postulated that in the frog an atmosphere of 4 per cent oxygen saturation caused constriction of the renal arterioles leading to anuria, and that denervation of the kidney did not prevent it (48). Van Slyke and his associates have confirmed that in contradistinction to other organs, the kidneys of dogs suffering from hemorrhagic shock do not increase oxygen extraction (49). This paradox has been explained tentatively by either the diversion of blood from cortex to the medulla (18) or by damage to the tubular cells from ischaemia (44). In a group of patients, a positive correlation between glomerular filtration rate and renal oxygen consumption was apparent. No correlation was evident between oxygen consumption and the degree of tubular reabsorption of water as measured by the inulin U/P ratio (50). The variability of oxygen consumption within the course of an experiment is noted, and the effects of altitude anoxia on renal function studied in the dog (51, 52). A renal vasoconstriction of central nervous origin elicited by anoxia has been postulated in dogs (53). Other experiments seem to indicate that either diffuse peripheral sympathetic discharge or massive discharge of epinephrine are involved in the anoxic condition (54). Hypoxia has been thought to be the cause of edema in congestive heart failure in man (55). Relation between excretory activity of the kidney and oxygen uptake in rats is evoked by Dock (56). By direct observations on skiagrams in artificially induced hypoxemia Fry has studied the behaviour of blood vessels in rabbits and found marked dilatation of the femoral blood vessels (57).

*Transient renal ischaemia.*—Complete renal ischaemia, obtained by clamping the renal artery in anaesthetised white rats for more than 2 hr., was uniformly fatal. The principal morphological change was necrosis of the descending segments of the proximal

convoluted tubules (58). Three of six dogs survived 4 hr. renal ischemia, and the conclusion offered was that renal failure in shock is of ischaemic nature (59). Bywaters insists that "crush syndrome" and mismatched transfusion anuria is not due to ischaemia or to vascular spasm, but is attributable to pigment precipitation. His main argument is the localization of damage to the distal convoluted tubules in both conditions (60). Oliver [see Van Slyke *et al.* (61)] found that in dogs, following 2 hr. of renal ischaemia, the glomeruli appeared normal, whereas in the distal convoluted tubules there were changes resembling those seen in cases of uremia following the "crush syndrome." Hemoglobin injected intraperitoneally into rats caused little structural damage to the kidney, and it was not until large amounts of hemoglobin were present within the lumina of the nephrons that injury became noticeable (62). Rigdon, working with monkeys infected with *Plasmodium knowlesi*, studied the hemoglobinuria and concluded that tubular degeneration results from the acidosis that accompanies the disease and is not the result of casts that form in the lumina of the tubules (63). The importance of acidosis has already been emphasized (64, 65). Previous dehydration has been considered to be an essential part of the process of producing hemoglobinuria nephrosis in the rabbit (66).

*Renal glycosuria.*—A review of the literature and report of four new cases of renal glycosuria has been published by Bland (67). Brush suggests that widespread vascular lesions due to repeated hemolytic streptococcal infection may well produce changes in the blood supply to the renal tubules which in turn could alter tubular physiology (187). A significant increase of the blood sugar in the renal vein, as compared with the aorta, was found in the nephrectomized rat that had been allowed to fast for four days; this was true particularly after evisceration (68). If no insulin was given, rats infused with glucose for 2 hr. after nephrectomy and evisceration exhibited a lower average terminal level of blood glucose than did the non-nephrectomized, uneviscerated animals (69). In the eviscerated dog the concentration of sugar was found to be greater in the renal vein than in the arterial blood, confirming the point that the kidney may be a source of blood sugar (70).

#### WATER DIURESIS

In the fasting dog, under the influence of water diuresis, great and rapid fluctuation in the rate of urea production has been ob-

served. An adrenocortical disturbance has been suspected (71). The effects of emotional disturbance on water diuresis and renal blood flow in the rabbit have been investigated. In the absence of renal ischemia, variations in urine flow appear to be mediated independently of the filtration rate, as they are in man and dog. Emotional stress and painful stimuli during water diuresis caused decreased urine flow, effective plasma flow and filtration rate, and a gradual increase in the creatinine U/P ratio, representing increased tubular reabsorption. Along with this, blood pressure increased from 5 to 20 mm. Hg. Denervation of the kidney did not change the response to painful stimuli. In contrast to the findings in dogs (72), vasomotor changes in the rabbit are considered to be responsible, initially, for the reduction of urine flow. The possibility that under these experimental conditions, the blood bypasses the cortex is discussed (73). The excretion of chloride in dogs was found to be increased during diuresis produced by the continuous intravenous injection of either 50 per cent sucrose, 50 per cent glucose, 5 per cent sorbital, or 10 per cent urea. Creatinine clearances revealed that as the urine volume increased there was a decreasing reabsorption of chloride from the tubular filtrate. Administration of pitressin or desoxycorticosterone did not modify the results (74). A group of patients with inadequate urinary water during the control hour of the experiment increased their total renal sodium excretion during water diuresis, whereas, in cases with adequate urine volume, total renal sodium excretion usually decreases. Certain xanthine drugs and a mercurial (mercuriophylline) seem to depress tubular reabsorption of sodium more than of water (75). O'Connor insists that inhibition of water diuresis by a hormone from the posterior lobe of the pituitary is brought about without change in the blood flow through the kidney. Of 21 normal bitches, the typical inhibition appeared consistently in only three and was not produced in any tests of seven. After denervation of the kidneys and suprarenals, inhibition of water diuresis occurred with all animals in the tests of the effects of emotional stress. This is believed to be due to the lack of release of epinephrine from the suprarenals during emotion after partial sympathectomy (76). Harris has again contributed to the study of water metabolism by the stimulation of the hypothalamus and pituitary gland in the unanaesthetized rabbit by means of the remote control method (77). He considers that "neurovascular" control of the anterior pituitary through the hypophyseal portal vessels is responsible for

the activity of the gland. The possibility of changes in the caliber of these vessels as the deciding factor is advanced. It is stated that the hypothalamus controls the neurohypophysis by means of the supraoptico-hypophyseal tract and that stimulation of this tract results in release of the antidiuretic hormone and inhibition of a water diuresis (78). Work on the excretion of an antidiuretic substance by the kidney has been reported (79). More work on the effect of "vasodepressor material" (VDM), isolated by Shorr & Zweifach (134), on water diuresis has been brought forward. Infusion of VDM preparation in dogs resulted, within 10 to 15 min., in a 70 to 80 per cent reduction in urine flow (80). Crystalline VDM has recently been identified with ferritin (81).

#### THE RENAL CIRCULATION

The results of studies of the renal circulation, initiated at Oxford (82) and prosecuted there by a group of workers, have been subjected to close scrutiny. These authors postulated that the blood reaching the kidney has two potential routes through that organ and, according to circumstances, it may pass almost exclusively by one or other of these routes (83 and 18). Gerbi insists on the part played by the nervous system in renal pathology and considers that the implications of an intrarenal vascular short circuiting may be far reaching (84). Muylder has published a monograph (85) on the nerve supply of the kidney, based in part on his personal findings, using the method of silver impregnation of Cajal and others. His conclusions, based mainly on morphology, are confirmative of part of the investigation of the Oxford workers. Measuring renal blood flow either by a rotameter in the renal artery of dogs or by the renal extraction of *p*-aminohippurate, Reubi *et al.* have found that after an intravenous injection of epinephrine the renal arteriovenous oxygen difference decreased almost regularly 3 to 8 min. later; and the same result was recorded in some, but not in all, human beings subjected to the action of epinephrine (0.5 mg.). About 20 min. after injection the extraction of PAH fell slightly. They conclude that renal arteriovenous by-passes may at times appear under some conditions but are not of great importance in the renal circulation (86). In a study of functional patterns in renal disease, Corcoran *et al.* found that in severe shock, the interpretation of the pattern is obscured, partly because of the redistribution of the renal blood, which may be largely dependent

upon altered permeability of tubules due to prolonged renal ischemia, but may also depend on shunting of the blood from renal cortex to medulla (87). The effect of a wire tourniquet applied for  $4\frac{1}{2}$  to 5 hr. to one of the hind limbs of rabbits has confirmed the redistribution of the intrarenal blood. This redistribution could be prevented by the injection of tetraethylammonium bromide in a dosage of 0.2 ml. per kg. of body weight (88). Working with cats and rabbits, the effect of the shunt on renal function has been determined by inulin and *p*-aminohippurate clearances. Sciatic nerve stimulation was used as the means of bringing the shunt into operation. About half the rabbits and a smaller proportion of cats showed a fall in PAH clearance as well as in inulin clearance, this being smaller. Slight increase in systemic blood pressure was noted in cats. By measuring directly the renal blood flow in cats, these authors observed a high total blood flow at the time of the reduction in PAH extraction and, in one case, when the blood pressure of the renal vein was high. They conclude that they have found some evidence that in cats as well as in rabbits appropriate stimulation leads in some animals to profound alterations in PAH and inulin clearances which may correspond to the presence of the "Oxford shunt" (89). Glass spheres of known size were injected into the renal arteries of normal human kidneys post-mortem, and the existence of arteriovenous anastomoses was indicated by recovery from the renal vein of spheres with diameter many times greater than the average diameter of a capillary. During life, spheres were recovered from the renal vein of anaesthetized rabbits and dogs (90). The neural control of the "renal shunt" has been studied in rabbits and cats and its efferent path was seen to be via the splanchnic roots; the initial response in rabbits and cats to stimulation of a spinal afferent is unilateral and with continuous stimulation it becomes bilateral in 5 to 10 min. in cats and in 3 to 5 hr. in rabbits. The crossing occurs in the cord; and anuria, which follows an approximation of the "crush syndrome" in cats, can be relieved by procaine block of the splanchnics (91). In cases with increased medullary circulation, Tortella (92) believes that the dilatation of the vasa recta explains the unconfirmed findings of interlobar and interlobular arteriovenous anastomoses mentioned by Geberg (190) and Golubew (189). In dogs and monkeys, Goodwin *et al.* have found that the exclusion of the cortical circulation may also be elicited by stimulation of the sciatic and splanchnic

nerves (93). The results are not uniformly positive, a fact found also in rabbits (18).

*Renal cortical necrosis.*—Renal cortical necrosis due to choline deficiency might be caused by circulatory disturbances, as necrosis occurs earliest in those portions of the functional units farthest removed from the source of blood supply (94). This is supported by the similarity of the vascular lesions seen in pyridine liver necrosis (95). Sick cell disease of the negro race, causing vascular obstruction by accumulation of sickle shaped erythrocytes, has been responsible for renal cortical necrosis (96, 97). The difference between the two renal circulations is indicated by the preservation of the medulla in these cases. In another case, only necrosis of the renal pelvis was caused (98).

*Adrenals and renal function.*—The mechanisms of desoxycorticosterone action have been investigated in rats and dogs, and their relation to fluid, sodium chloride intake, and blood pressure evaluated (99 to 102). Some of this work supports the views of Selye on the hypertensive action of desoxycorticosterone (142). A fall in the oxygen supply of the adrenals of the dog led to a rise in epinephrine output. Splanchnic stimulation caused an increase in the liberation of epinephrine by the gland only when the epinephrine content of the arterial blood was increased (103). Unilateral adrenalectomy affected homolateral renal function of dogs only in so far as the renal nerves were injured; it was not possible to locate the site of the vascular readjustment which must take place to cause an increase in renal blood flow and glomerular filtration rate subsequent to unilateral adrenalectomy or splanchnectomy (104). In cases of adrenal insufficiency, maximum excretory capacity was reduced and was not affected by hormone therapy. Filtration rates were reduced, and it was postulated that this is secondary to reduction in renal plasma flow (105). On stimulating the splanchnic nerves of spinal cats, from which the viscera have been removed and the kidneys excluded from the circulation, only impulses to the suprarenal medulla are produced. A mixture of both epinephrine and norepinephrine (arterenol) is liberated (106). Sympathin is a mixture of both epinephrine and norepinephrine in variable proportions (107).

#### NEPHRITIS AND NEPHROSIS

Reader could not confirm the previous work of causing nephritis in rats by injecting blood from nephritic patients (108). In

cases of acute nephritis, the diodrast clearance was much less reduced in the acute stage than the inulin clearance, so that the filtration fraction was notably lowered. The possibility of an intrarenal vascular shunt operating in this case is discussed and some objections raised (109). Renal filtration rates in toxæmia of pregnancy, estimated by inulin and creatinine clearances, suggest that an angiospasm may be responsible for the oliguria and anuria (110). In four cases of oliguria after abortion which recovered, both glomerular and tubular function were equally and almost totally suppressed. The explanation given is that there is a redistribution of intrarenal blood, shunting the cortex; but even if this is so, the trigger factors in these cases remain obscure (111). A disturbance in protein metabolism characterized by hyperglobulinemia has been found during toxæmia of pregnancy (112). Significant abnormalities in the concentration of electrolytes in plasma and urine in children with nephritic edema are described, and emphasis is placed on the rapid changes in plasma sodium and bicarbonate concentration (113). Beryllium poisoning caused renal lesions almost entirely limited to the distal portion of the proximal convoluted tubules, but in some cases the entire proximal convoluted tubule was damaged (114). Barbiturate poisoning caused oliguria and a rise of blood urea which was frequently associated with shock. A histological picture of "lower nephron nephrosis" was found (115). The damage caused by bichloride of mercury was very largely confined to the epithelium of the proximal convoluted tubule. Uranium nitrate caused a similar lesion, but the distal convolution may show evidence of delayed implication. Administration of 15 mg. of BAL (2,3-dithiopropanol) per kg. of body weight at 12 hr. intervals for two days was found to increase the severity of the lesions in dogs (116). Unsaturated sodium morrhuate, injected into the renal artery of heparinized dogs with the renal circulation temporarily interrupted, caused necrosis of the epithelium of the tubules when the injury to the vessel walls was negligible (117). In dogs intoxicated by alcohol administered by stomach tube, both cortical glomeruli and the tubules were enlarged and, in advanced states, the latter were fibrotic and shrunken. These lesions may be secondary to hepatic lesions (118). Two cases of glomerulonephritis with minimal glomerular changes and masquerading clinically as "lipid nephrosis" suggest the possibility that a glomerulonephritis may resolve, leaving the glomeruli intact (119). Dogs fed on a high fat diet for two months or longer, in

which renal insufficiency had been induced experimentally, regularly suffered arterial lesions. These can be prevented by the administration of vitamin E (120). An "antiretentional" diet, rich in proteins and vitamins and restricted in fats, carbohydrates, salt, and fluid, has often reduced the blood pressure of hypertensive patients (121). A case of renal dwarfism with hypothyroidism was found at necropsy to be affected by marked atrophy of the kidneys (122). Leiter has given a pertinent classification of the renal functional diseases (123).

#### HYPERTENSION: ITS RELATION TO THE KIDNEY

Sabin has analysed one hundred cases of unilateral renal disease in which nephrectomy caused a substantial lowering of the blood pressure. The most common renal disease was pyelonephritis (124). Effersoe, commenting on the results of nephrectomy in two hundred reported cases of hypertension, doubts the efficiency of nephrectomy and quotes two personal cases with poor results (125). A good result three years after nephrectomy is reported elsewhere (126). Thirty five cases out of 61 of another series were "greatly" benefited by nephrectomy up to two years after the operation, and 15 cases, after five years. Infection was found in all kidneys removed, but the exact histological changes which cause the rise of blood pressure have not yet been found. Excretory urography is the best single method for diagnosis (127). In general, it may be said that nephrectomy can bring hypertension at least temporarily under control, but this is far from frequent. It seems less disputable that the kidney may be responsible for a persistent rise of arterial blood pressure.

*Factors responsible for hypertension; their effect on kidney function.*—Goldblatt and his associates report the demonstration and identification of hypertensin in the systemic blood of dogs in the earlier period of experimental renal hypertension (128). But the *in vivo* renin effect is believed to be inadequately explained by the formation of hypertensin (129). The effect of renin on proteinuria and PAH clearance at low plasma levels has been studied in rabbits; it is suggested that renin diminishes tubular reabsorption of protein, causes a significant fall in the effective plasma flow rate, and raises the filtration fraction, probably by efferent arteriolar constriction (130). These conclusions are not dissimilar to those

reported by Pickering & Prinzmetal (131). The ability of hypertensinase to destroy hypertensin has stimulated the investigation on plant hypertensinase. Injected intravenously, an isoelectric and ammonium sulphate preparation of hypertensinase from wheat bran caused the blood pressure of hypertensive dogs to fall (132). In the plasma of cats previously subjected to hemorrhagic hypotension, Shipley & Helmer have detected what they believe to be a pressor substance which differs from renin in that it possesses the apparently unique ability to cause a sustained elevation of arterial blood pressure when injected intravenously into cats which have been nephrectomized from 6 to 48 hr. before. This substance is formed by the kidneys, presumably as the result of decreased blood flow or lowered blood pressure. It is called "sustained pressor principle" (S.P.) (133).

A substantial number of papers have increased our knowledge of the part played by VDM and VEM (vasoexcitor material) in the production of shock and the regulation of blood pressure, and also in hypertension (134 to 138). The fact that these principles are formed under anaerobic conditions and are inhibited under aerobic conditions strongly suggests that some degree of renal ischaemia intervenes in their formation, perhaps as Shorr mentions, of neurogenic nature. Adrenalectomy abolishes VEM formation; this can be restored by desoxycorticosterone acetate (DOCA) (139). VEM has been found to be formed by the renal cortical tissue (140).

The role attributed to the adrenal cortex, that of safeguarding the glomerular filtrate through its pressor hormone, has determined the study of the adrenals in 55 cases of essential hypertension, 15 cases of renal hypertension, and 57 more hypertensive controls coming to necropsy. The hypertensive cases had the adrenal cortical lipid increased, giving a picture opposite to that of Addison's disease (141). H. Seyle explains by the general-adaptation syndrome a rise in the corticotropin secretion which causes enlargement of the adrenal cortex with signs of increased corticoid production (142). In hypertensive patients F. L. Selye finds an increase in the ratio of serum sodium to chlorine, expressed as Na/Cl, which is apparently never found in patients with normal blood pressure and which he thinks may be related to an abnormal adrenal cortical hormone production (143). The effect of DOCA on blood pressure, renal function, and electrolyte pattern in the

intact rat has been investigated. The pattern of renal functional change seems remarkably similar to that observed in essential hypertension in man. With DOCA and saline, the process was progressive, while in those animals receiving DOCA alone, the vascular spasm and renal ischaemia disappeared (144). In a study of 58 subjects with essential hypertension Wolf *et al.* conclude that essential hypertension in these patients was the result of a reaction pattern to stress which causes renal vasoconstriction. After thoracolumbar sympathectomy, the efferent glomerular constriction in response to situational threats is abolished, but the afferent arteriolar constriction still persists, suggesting an intrinsic humoral mechanism (145). Simultaneous determinations of cardiac output by right heart catheterization and renal blood flow by using *p*-amino-hippurate clearance in 18 normal and 18 hypertensive subjects showed the average cardiac output to be the same, whereas the renal blood flow varied from normal to very low values, and renal fractions decreased to as low as 1.4 per cent in severe hypertension (146).

Using tetraethylammonium chloride (TEAC), a comparative study has been made of the blood pressure response during and after recovery from toxæmia of pregnancy. Whereas in normal term pregnancy TEAC reduces mean blood pressure floor very strikingly, in cases of toxæmia of pregnancy, only moderate responses were obtained, suggesting a humoral mechanism to be involved in these cases. An increase in venous resistance, caused by the uterine pressure, cannot be the factor responsible, as it would have been equally present in both cases (147). Cold pressor tests were prevented from further raising the blood pressure in hypertensive patients by the use of TEAC or by spinal anaesthesia at T 3 level. A delayed response which occurred in 12 out of 20 patients can be explained by a humoral mechanism. The data suggest that both neurogenic and humoral mechanism may be involved (148).

In hypertensive man and dog, spinal anaesthesia at T 5 commonly results in a decrease of arterial pressure and an increase of minimal plasma flow to average 1.2 times normal in man. Taylor, Corcoran & Page conclude that the maintenance of experimental renal, as of clinical arterial, hypertension is partially dependent on an unidentified vasomotor outflow from the upper thoracic spinal cord (149). Takats (151), on the basis of his clinical experience,

merges into a single group the "diencephalic" hypertensive syndrome described by Page (150) and the endocrine type of hypertension and considers it often impossible to differentiate a renal from a neurogenic type of hypertension. Vasopressin, mobilised from the posterior pituitary gland, is identical to the antidiuretic hormone, thus acting directly on both the kidneys and the peripheral vascular bed (151).

The recent isolation of the sympathicolytic from the purely oxytocic principle contained in ergot has opened a new field of investigation in essential hypertension. Rothlin (152) and Stoll (153) have been mainly responsible for this most interesting development. The dihydroalkaloids, dihydrocornine (DHO 180), dihydroergocristine (DCS 90), and dihydroergokryptine (DHK 135) inhibit, or entirely suppress, vasomotor sympathetic and adrenergic impulses to the peripheral vessels in doses of 0.3 to 0.5 mg. subcutaneously, intravenously, or intra-arterially. In hypertensive patients, both systolic and diastolic blood pressure may be brought under control by the use of the combination of three drugs (Hydergine) (154). In trained, anaesthetized dogs, after bilateral denervation performed several weeks before, injection of 2 to 6 mg. per hr. caused a rise in blood pressure of approximately 25 mm. Hg., together with a reduction in renal plasma flow and glomerular filtration, which has been taken as a criterion for renal vasoconstriction. When 0.2 mg. to 0.25 mg. of DHO 180 was administered, epinephrine did not alter the blood pressure and renal function (155). It has been found, by the use of the Goetz optical digital plethysmograph, that DHO 180 does not contain the vasoconstrictive principle of ergot which is still present in dihydroergotamine (156). The effect of dibenamine in blood pressure has also been investigated in hypertensive patients and found to cause lowerings of blood pressure which may last 72 hr. (157).

*Renal changes in hypertension.*—Schloss has studied, in a number of papers, the histological changes caused in the rat made hypertensive by the constriction of one of the renal arteries. The vascular lesions are considered to be due primarily to the mechanical action of high blood pressure; but the possibility that renin or angiotonin might have, in addition to its pressor effect, an allergizing action is suggested (158). Hypertension of this type can exist without any histological lesion of the constricted kidney. The renal tubules seem to play an important part in the production of renin

(159). In only a few cases of extreme atrophy due to ischaemia of the kidney do the afferent arterioles and interlobular arteries demonstrate a considerable increase in number and size of the juxtaglomerular E-cells. It seems likely that hypoxia is the factor responsible for the degeneration of muscle cells (160). This has also been postulated by Goormaghtigh (161). Byrom & Dodson insist that overstretching of the vascular wall may be the cause of damage in hypertension. In rats they have also seen blanching of the surface of the renal cortex after the intracarotid injection of warm Ringer's solution forcibly injected. The frequent occurrence of vascular spasm is noted. Its part in the causation of necrotizing arterioles is not stressed (162). Trueta considers renal cortical spasm and its consequence, dilatation of the medullary circulation, to be responsible for the altered hemodynamics which underlie persistent raising of arterial blood pressure (163). While investigating the relationship between arterial pressure and renal blood flow in a preparation consisting of two vascularly connected dogs, it has been found that a permanent decrease in PAH clearances occurred early in the course of lowering the blood pressure (164). In hypertensive patients, it has been found that there is a close correlation between falls in blood pressure induced by high spinal anaesthesia and inulin and diodrast clearances. This correlation occurs in patients with either normal or impaired renal function (165). A detailed study of the nerve supply of the kidney and its therapeutic importance in hypertension has been published by Mitchell (166). A meticulous denervation technique, described by Dobritz, includes division of the greater and lesser splanchnic nerves, removal of the splanchnic, suprarenal, semilunar, and aorticorenal ganglia, decapsulation of the kidneys, and resection of the upper lumbar sympathetic ganglia (167). Monographs on experimental renal hypertension by Page & Corcoran (168) and by Goldblatt (169) on the renal origin of hypertension contribute considerably to the understanding of this problem. Addis dealt extensively in book form with the problem of glomerular nephritis and its relation to kidney function and hypertension (170).

A comprehensive study of kidney function in renal disorders and in hypertension has been contributed by Hogeman (188), using clearance tests. He suggests that the changes observed during and

after shock might be explained by the juxta-medullary "by-pass," an explanation which he thinks might also be applied to cases of old-standing hypertension. He does not think that the same mechanism might explain the changes observed in acute nephritis, when the renal blood flow and tubular function are less affected than glomerular filtration.

#### ANURIA AND ITS TREATMENT

In posttransfusion anuria, unilateral decapsulation may sometimes be followed immediately by diuresis and eventual recovery. The mechanism of action of capsulectomy is believed to be the removal of sympathetic nerve impulses, but it might also be due to the effect of spinal anaesthesia used in many of these cases (171). The part played by cortical vascular spasm in the production of anuria is also stressed by Darmady after studying seventeen cases of post traumatic uremia. The maximum epithelial tubular damage was found in the ascending and descending loops of Henle (172). That traumatic uremia and the crush syndrome cause identical lesions in the kidney and that myoglobinuria is not an essential part of them, is suggested by three cases reported by Hicks (173). Appropriate intake and an artificial kidney, used only when it was clear that the renal cortex had been permanently damaged, prolonged life for 28 days in a patient with postpartum renal cortical necrosis (174). In a series of eight patients with anuria, treated with Alwall's dialysis, two survived (175). Two recoveries out of three cases have also been reported (176). Peritoneal irrigation was successful as a dialyzing procedure in a case of mercurial nephrosis after five days of lavage (177). Another successful result was obtained in a 10 year-old boy affected by uremia due to acute nephritis after scarlet fever (178). In 53 reported cases of anuria, of those in whom peritoneal lavage was used, 13 survived (179). Intestinal perfusion of 23 l. of fluid in 12 hr. by means of Miller-Abbott tubes caused the blood nonprotein nitrogen to drop from 330 mg. per ml. to 121 mg. and 12 hr. later to 66 mg. (180). The advantages of this method over the "artificial kidney" and peritoneal lavage have been stressed (181).

The use of intravenous procaine, 10 ml. of a 1 per cent solution administered in 5 min. and repeated in 6 hr., has been followed by a resolution in two cases of eclamptic anuria (182). Three success-

ful administrations of intravenous procaine are reported by Friis. One of the cases had a new acute attack of anuria and the administration of intravenous procaine failed to save the patient (183).

The intravenous infusion of concentrated human serum albumin often produces a transient diuresis in patients with nephrosis. Plasma flow is increased. It changes the renal hemodynamics with functional impairment of the cells of the proximal convoluted tubules. A diversion of the intrarenal blood from the cortex to the medulla is thought to be the cause of the decreased extraction of PAH and the decreased filtration fraction observed. The two patients who showed the greatest and most prolonged fall in PAH extraction following albumin administration were affected by advanced renal disease, and the juxtamedullary shunts are prominent in these cases (184).

## LITERATURE CITED

1. BARNETT, H. L., HARE, K., McNAMARA, H., AND HARE, R., *J. Clin. Invest.*, **27**, 691-99 (1948)
2. BARNETT, H. L., McNAMARA, H., HARE, R. S., AND HARE, K., *Federation Proc.*, **7**, 5-6 (1948)
3. BARNETT, H. L., HARE, W. K., McNAMARA, H., AND HARE, R. S., *Proc. Soc. Exptl. Biol. Med.*, **69**, 55-57 (1948)
4. WEST, J. R., SMITH, H. W., AND CHASIS, H., *J. Pediat.*, **32**, 10-18 (1948)
5. OSTER, J., *Acta Med. Scand.*, **129**, 513-23 (1948)
6. HARE, K., UNGEWITHER, L., BARNETT, H. L., AND McNAMARA, H., *Federation Proc.*, **7**, 51 (1948)
7. FUHRMANN, G., AND SCHUBERT, H., *Z. ges. inn. Med.*, **2**, 541-44 (1947)
8. JOSEPHSON, B., *Acta Med. Scand.*, Suppl. 196, 239-49 (1947)
9. JOSEPHSON, B., *Acta Med. Scand.*, **128**, 514-37 (1947)
10. PITTS, R. F., LOTSPEICH, W. D., SCHIESS, W. A., AND AYER, J. L., *J. Clin. Invest.*, **27**, 48-56 (1948)
11. BERLINER, R. W., KENNEDY, T. J., JR., AND HILTEN, J. G., *Am. J. Physiol.*, **154**, 537-41 (1948)
12. MUDGE, G. H., FOULKS, J., AND GILMAN, A., *Proc. Soc. Exptl. Biol. Med.*, **67**, 545-47 (1948)
13. BERLINER, R. W., AND KENNEDY, T. J., JR., *Proc. Soc. Exptl. Biol. Med.*, **67**, 542-45 (1948)
14. DICKER, S. E., *J. Physiol. (London)*, **107**, 8-13 (1948)
15. WESSON, L. G., ANSLOW, W. P., JR., AND SMITH, H. W., *Federation Proc.*, **7**, 133 (1948)
16. WILLS, J. H., AND MAIN, E., *Am. J. Physiol.*, **154**, 220-228 (1948)
17. LIPPMAN, R. W., *Am. J. Physiol.*, **152**, 27-35 (1948)
18. TRUETA, J., BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., AND PRICHARD M. M. L., *Studies of the Renal Circulation*, 187 pp. (Blackwell Scientific Publications, Oxford, 1947)
19. HUBER, G. C., *Am. J. Anat.*, **6**, 391-406 (1907)
20. FUCHS, F., *The Flow of Water through the Kidney*, 67 pp. (Manhattan Printing Co., New York, 1944)
21. BARCLAY, J. A., COOKE, W. T., AND KENNEY, R. A., *Am. J. Physiol.*, **151**, 621-25 (1947)
22. CHAPMAN, C. B., HENSCHER, A., MINCKLER, J., FORSGREN, A., AND KEYS, A., *J. Clin. Invest.*, **27**, 639-44 (1948)
23. WHITE, H. L., AND ROLF, D., *Federation Proc.*, **7**, 133 (1948)
24. WHITE, H. L., AND ROLF, D., *Am. J. Physiol.*, **152**, 504-16 (1948)
25. CHAPMAN, C. B., HENSCHER, A., AND FORSGREN, A., *Proc. Soc. Exptl. Biol. Med.*, **69**, 170-71 (1948)
26. MERRILL, A. J., AND CARGILL, W. H., *J. Clin. Invest.*, **27**, 272-77 (1948)
27. MOKOTOFF, R., ROSS, G., AND LEITER, L., *J. Clin. Invest.*, **27**, 1-9 (1948)
28. HICKAM, J. B., CARGILL, W. H., AND GOLDEN, A., *J. Clin. Invest.*, **27**, 290-98 (1948)
29. TALSO, P. J., CROSLLEY, A. P., JR., AND CLARKE, R. W., *Federation Proc.*, **7**, 122 (1948)

30. FRENCH, D. M., MOLANO, P. A., AND BOOKER, W. M., *Federation Proc.*, **7**, 38 (1948)
31. BRADLEY, S. E., HALPERIN, M. H., AND MAYER, H., *J. Clin. Invest.*, **27**, 635-38 (1948)
32. HONCK, C. R., BING, R. J., CRAIG, F. N., AND VISSCHER, F. E., *Am. J. Physiol.*, **153**, 158-68 (1948)
33. HIATT, E. P., AND SUHRIE, V., *Am. J. Physiol.*, **148**, 684-88 (1947)
34. OVERMAN, R. R., AND WANG, S. C., *Am. J. Physiol.*, **148**, 289-95 (1947)
35. WANG, S. C., *Am. J. Physiol.*, **148**, 547-56 (1947)
36. WANG, S. C., AND OVERMAN, R. R., *Ann. Surg.*, **129**, 207-22 (1949)
37. WIGGERS, H. C., INGRAHAM, R. C., ROEMHILD, F., AND GOLDBERG, H., *Am. J. Physiol.*, **153**, 511-20 (1948)
38. FRANCK, C., GRANDPIERRE, R., ARNOULD, P., AND DIDON, P., *Compt. rend. soc. biol.*, **152**, 79-82 (1948)
39. KALK, H., AND BRÜHL, W., *Klin. Wochschr.* **22**, 25 (1943)
40. FRANKLIN, K. J., *Proc. Soc. Exptl. Biol. Med.* **71**, 339 (1949)
41. DZIEMIAN, A. J., *Federation Proc.*, **7**, 29 (1948)
42. MOON, V. H., *Am. J. Path.*, **24**, 235-74 (1948)
43. SANDERSON, P. H., *Clin. Sci.*, **6**, 207-22 (1948)
44. VAN SLYKE, D. D., *Ann. Internal Med.*, **28**, 701-22 (1948)
45. HERBERT, P. A., *Ann. Internal Med.*, **15**, 648-62 (1948)
46. LUCKÉ, B., *Military Surgeon*, **99**, 371-96 (1946)
47. BARCROFT, J., AND BRODIE, T. G., *J. Physiol. (London)*, **32**, 18-27 (1905); **33**, 52-68 (1905)
48. ADOLPH, E. P., *Am. J. Physiol.*, **108**, 177 (1934)
49. DOLE, V. P., EMERSON, K., JR., PHILLIPS, R. A., HAMILTON, P., AND VAN SLYKE, D. D., *Am. J. Physiol.*, **154**, 337-45 (1946)
50. CARGILL, W. H., AND HICKAM, J. B., *J. Clin. Invest.*, **27**, 528 (1948)
51. McDONALD, R. K., AND KELLEY, V. C., *Am. J. Physiol.*, **154**, 193-206 (1948)
52. KELLEY, V. C., AND McDONALD, R. K., *Am. J. Physiol.*, **154**, 201-6 (1948)
53. MALMEJAC, J., CHARDON, G., AND GROSS, A., *J. Physiol.*, **40**, 247a-49a (1948)
54. MARSH, D. F., AND VAN LIERE, E. J., *J. Pharmacol. Exptl. Therap.*, **94**, 221 (1948)
55. BRIGGS, A. P., FOWELL, D. M., HAMILTON, W. F., REMINGTON, J. W., WHEELER, N. C., AND WINSLOW, J. A., *J. Clin. Invest.*, **27**, 810-17 (1948)
56. DOCK, W., *New Engl. J. Med.*, **236**, 773-82 (1947)
57. FREY, J., *Klin. Wochschr.*, **26**, 42-43 (1948)
58. KOLETSKY, S., AND GUSTAFSON, G. E., *J. Clin. Invest.*, **26**, 1072-78 (1947)
59. HAMILTON, P. B., PHILLIPS, R. A., AND HILLER, A., *Am. J. Physiol.*, **152**, 517-22 (1948)
60. BYWATERS, E. G. L., *Lancet*, **254**, 301 (1948),
61. VAN SLYKE, D. D., PHILLIPS, R. A., HAMILTON, P. B., ARCHIBALD, R. M., DOLE, V. P., AND EMERSON, K., JR., *Trans. Assoc. Am. Physicians*, **58**, 119-27 (1944)
62. RATHER, L. J., *J. Exptl. Med.*, **87**, 163-73 (1948)
63. RIGDON, R. H., *Am. J. Path.*, **24**, 701 (1948)
64. LALICH, J. J., *J. Exptl. Med.*, **87**, 157-62 (1948)

65. BING, R. J., *Proc. Soc. Exptl. Biol. Med.*, **53**, 29-30 (1943)
66. BYWATERS, E. G. L., AND STEAD, J. K., *Quart. J. Exptl. Physiol.*, **33**, 53-70 (1944)
67. BLAND, J. H., *Arch. Internal Med.*, **29**, 461-468 (1948)
68. REINECKE, R. M., RUDOLPH, G. G., BRYSON, M. J., AND SAMUELS, L. T., *Am. J. Physiol.*, **153**, 46-54 (1948)
69. INGLE, D. J., AND NEZAMIS, J. E., *Am. J. Physiol.*, **153**, 393-96 (1948)
70. REINECKE, R. M., AND HANSER, P. J., *Am. J. Physiol.*, **153**, 205-9 (1948)
71. OGDEN, E., AND TRIPP, E., *Am. J. Physiol.*, **153**, 190-96 (1948)
72. O'CONNOR, W. J., AND VERNEY, E. B., *Quart. J. Exptl. Physiol.*, **33**, 77-90 (1945)
73. BROD, J., AND SIROTA, J. H., *Am. J. Physiol.*, **157**, 31-39 (1949)
74. CIZEK, L. J., AND HOLMES, J. H., *Federation Proc.*, **7**, 21 (1948)
75. CRUTCHFIELD, A. J., AND WOOD, J. E., JR., *Ann. Internal Med.*, **28**, 28-40 (1948)
76. O'CONNOR, W. J., *Proc. Roy. Soc. Med.*, **41**, 666-70 (1948)
77. HARRIS, G. W., *Philos. Trans. B.*, **232**, 385-441 (1947)
78. HARRIS, G. W., *Proc. Roy. Soc. (London)*, **41**, 661-68 (1948)
79. HARRIS, G. W., *J. Physiol. (London)*, **107**, 430-35 (1948)
80. BAEZ, S., MAZUR, A., AND SHORR, E., *Federation Proc.*, **7**, 5 (1948)
81. MAZUR, A., AND SHORR, E., *J. Biol. Chem.*, **176**, 771-87 (1948)
82. TRUETA, J., *Lancet*, **249**, 415 (1945)
83. TRUETA, J., BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., AND PRICHARD, M. M. L., *Lancet*, **251**, 237-38 (1946)
84. GERBI, C., *La Settimana Med.*, **35**, 41-44 (1947)
85. DE MUYLDER, C., *La contribution du tissu nerveux à la constitution du rein et ses conséquences en pathologie*, 148 pp. (Université Catholique de Louvain, 1948)
86. REUBI, F. C., SCHROEDER, H. A., AND WILLIAMS, A. H., *Federation Proc.*, **7**, 101 (1948)
87. CORCORAN, A. C., TAYLOR, R. D., AND PAGE, I. H., *Ann. Internal Med.*, **28**, 560-82 (1948)
88. STOCK, F. E., *Lancet*, **255**, 570 (1948)
89. BLACK, D. A. K., AND SAUNDERS, M. G., *Lancet*, **256**, 733-34 (1949)
90. SIMKIN, B., BERGMAN, H. C., SILVER, H., AND PRINZMETAL, M., *Arch. Internal Med.*, **81**, 115-25 (1948)
91. CORT, J. H., AND BARRON, D. H., *Federation Proc.*, **7**, 23 (1948)
92. PONS-TORTELLA, E., *Med. Clinica (Barcelona)*, **11**, 68-76 (1948)
93. GOODWIN, W. E., SLOAN, R. D., AND SCOTT, W. W., *J. Urol.*, **61**, 1010-27 (1949)
94. BAXTER, J. H., AND VAN SLYKE, D. D., *Federation Proc.*, **7**, 145 (1948)
95. BAXTER, J. H., *J. Nutrition*, **34**, 333-49 (1947)
96. KIMMELSTIEL, P., *Am. J. Med. Sci.*, **216**, 11-19 (1948)
97. BAUER, J., *Acta Med. Scand.*, **129**, 1-11 (1948)
98. ABEL, M. S., AND BROWN, C. R., *J. Am. Med. Assoc.*, **136**, 624-25 (1948)
99. GREEN, D. M., *J. Lab. Clin. Med.*, **33**, 853-54 (1948)
100. GREEN, D. M., COLEMAN, D. H., AND MCCABE, M., *Am. J. Physiol.*, **154**, 465-74 (1948)

101. SUMMERS, J. E., *Am. J. Physiol.*, **154**, 118-21 (1948)
102. FRIEDMAN, S. M., FRIEDMAN, C. L., AND POLLEY, J. R., *Am. J. Physiol.*, **153**, 226-36 (1948)
103. BULBRING, E., BURN, J. H., AND DE ELIO, F. J., *J. Physiol. (London)*, **107**, 222-32 (1948)
104. KRISS, J. P., FUTCHER, P. H., AND COLEMAN, M. L., *Am. J. Physiol.*, **154**, 229-40 (1948)
105. WATERHOUSE, C., AND KEUTMANN, E. H., *J. Clin. Invest.*, **27**, 372-79 (1948)
106. BULBRING, E., AND BURN, J. H., *Nature*, **163**, 363 (1949)
107. BACQ, Z. M., AND FISCHER, P. F., *Arch. Intern. Physiol.*, **55**, 73-91 (1947-48)
108. READER, R., *Brit. J. Exptl. Path.*, **29**, 248-55 (1948)
109. BLACK, D. A. K., PLATT, R., ROWLANDS, E. N., AND VARLEY, H., *Clin. Sci.*, **6**, 295-302 (1948)
110. ODELL, L. O., *Am. J. Med. Sci.*, **213**, 709-14 (1947)
111. HUMPHREY, J. H., AND AVERY JONES, F., *Clin. Sci.*, **6**, 173-86 (1948)
112. LINDEBOOM, G. A., *Acta Med. Scand.*, **131**, 368-79 (1948)
113. FOX, C. L., JR., AND McCUNE, D. J., *Am. J. Med. Sci.*, **216**, 1-10 (1948)
114. SCOTT, J. K., *Arch. Path.*, **45**, 354-59 (1948)
115. LOUIS, P., WULFF, M. H., GEORG, J., MØRCH, E. T., AND SONNE, L. M., *Ugeskrift Laeger*, **111**, 349-56 (1949)
116. MACNIDER, W. M. DE B., TROTT, J. C., JR., AND BRUCE, M. D., *J. Pharmacol. Exptl. Therap.*, **94**, 262-73 (1948)
117. MYLON, E., AND SMITH, E. R., *Arch. Path.*, **45**, 21-24 (1948)
118. CHAIKOFF, I. L., ENTENMAN, C., GILLMAN, Y., AND CONNER, C. L., *Arch. Path.*, **45**, 435-46 (1948)
119. MOSCHOWITZ, E., *Am. J. Med. Sci.*, **216**, 146-57 (1948)
120. HOLMAN, R. L., *Am. Heart J.*, **36**, 476 (1948)
121. FOLDES, E., *N. Y. State J. Med.*, **47**, 2699-2702 (1947)
122. ULLMANN, T. D., AND SCHORR, S., *Ann. Internal Med.*, **29**, 715-30 (1948)
123. LEITER, L., *Ann. Internal Med.*, **28**, 229-47 (1948)
124. SABIN, H. S., *J. Urol.*, **59**, 8-20 (1948)
125. EFFERSON, P., *Acta Med. Scand.*, **131**, 10-22 (1948)
126. SWEENEY, J. S., AND PACE, J. M., *Ann. Internal Med.*, **29**, 370-74 (1948)
127. BARKER, N. W., AND BRAASCH, W. F., *Surg. Gynecol. Obstet.*, **84**, 299-304 (1947)
128. GOLLAN, F., RICHARDSON, E., AND GOLDBLATT, H., *J. Exptl. Med.*, **87**, 389-400 (1948)
129. MYLON, E., LUND, M., AND HELLER, J. H., *Am. J. Physiol.*, **152**, 397-406 (1948)
130. BRANDT, J. L., AND GRUHN, J. G., *Am. J. Physiol.*, **153**, 458-64 (1948)
131. PICKERING, G. W., AND PRINZMETAL, M., *J. Physiol. (London)*, **98**, 314 (1940)
132. GOLLAN, F., RICHARDSON, E., AND GOLDBLATT, H., *J. Exptl. Med.*, **87**, 29-39 (1948)
133. SHIPLEY, R. E., AND HELMER, O. M., *Am. J. Physiol.*, **153**, 340-47 (1948)
134. SHORR, E., AND ZWEIFACH, B. W., *Trans. Assoc. Am. Physicians*, **61**, 350-60 (1948)
135. SHORR, E., ZWEIFACH, B. W., AND FURCHGOTT, R. F., *Ann. N.Y. Acad. Sci.*, **49**, 571-92 (1948)

136. ZWEIFACH, B. W., ROSENFELD, S., AND SHORR, E., *Federation Proc.*, **7**, 139 (1948)
137. ZWEIFACH, B. W., BAEZ, S., FURCHGOTT, R. F., AND SHORR, E., *Federation Proc.*, **7**, 139 (1948)
138. SHORR, E., ZWEIFACH, B. W., AND BAEZ, S., *Federation Proc.*, **7**, 115 (1948)
139. SHORR, E., *Am. J. Med.*, **5**, 783-91 (1948)
140. SHORR, E., *Am. J. Med.*, **4**, 120-29 (1948)
141. FISHER, J. A., AND HEWER, T. F., *J. Path. Bact.*, **59**, 605-13 (1948)
142. SELYE, H., *Textbook of Endocrinology*, 867 pp. (Acta Endocrinologica, Montreal Univ., Canada, 1947)
143. SELYE, F. L., *Can. Med. Assoc. J.*, **57**, 325-30 (1947)
144. FRIEDMAN, S. M., POLLEY, J. R., AND FRIEDMAN, C. L., *J. Exptl. Med.*, **87**, 329-38 (1948)
145. WOLF, S., PFEIFFER, J. B., RIPLEY, H. S., WINTER, O. S., AND WOLFF, H. G., *Ann. Internal Med.*, **29**, 1056-76 (1948)
146. BOLOMEY, A. A., BREED, E. F., MICHIE, A., MICHIE, K., AND LAWSON, H. D., *Federation Proc.*, **7**, 10 (1948)
147. BRUST, Z. Z., ASSALI, N. S., AND FERRIS, E. B., *J. Clin. Invest.*, **27**, 717-26 (1948)
148. REISER, M. F., AND FERRIS, E. B., JR., *J. Clin. Invest.*, **27**, 156-63 (1948)
149. TAYLOR, R. D., CORCORAN, A. C., AND PAGE, I. H., *Federation Proc.*, **7**, 123 (1948)
150. PAGE, I. H., *Am. J. Med. Sci.*, **190**, 9-14 (1935)
151. DE TAKATS, G., AND FOWLER, E. F., *Surgery*, **21**, 773-99 (1947)
152. ROTHLIN E., *Helv. Physiol. et Pharmacol. Acta.*, **2**, 48 (1944)
153. STOLL, A., *Experientia*, **1**, 250-62 (1945)
154. KAPPERT, A., *Helv. Med. Acta*, Suppl. 22[A]1, 1-163 (1949)
155. KUBICEK, W. G., KOTTKE, F. J., FELDER, D. A., LAKER, D. J., AND VISSCHER, M. B., *Festschrift Dr. E. Rothlin*, 476 pp. (Berro Schwabe and Co., Verlag, Basel, 1948)
156. BLUNTSCHLI, H. J., AND GOETZ, R. H., *Am. Heart J.*, **35**, 873-94 (1948)
157. HAIMOVICI, H., AND MEDINETS, H. E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 162-66 (1948)
158. SCHLOSS, G., *Schweiz. Z., Path. u. Bakt.*, **11**, 109-32 (1948)
159. SCHLOSS, G., *Helv. Med. Acta.*, **14**, 22-44 (1947)
160. SCHLOSS, G., *Acta Anat.*, **6**, 80-91 (1948)
161. GOORMAGHTIGH, N., *La Fonction Endocrine des Artérioles Rénales*, 110 pp. (Librarie R. Fonteyn, Louvain, 1944)
162. BYROM, F. B., AND DODSON, L. F., *J. Path. Bact.*, **60**, 357-68 (1948)
163. TRUETA, J., *Mém. acad. chir.*, **31**, **32**, 722 (1948)
164. BATTEN, W., OGLE, B. C., REPELA, C., HEGE, J. R., LITTLE, J. M., AND GREEN, N. D., *Federation Proc.*, **7**, 6 (1948)
165. GREGORY, R., LEVIN, W. C., ROSS, G. T., AND BENNETT, A., *Arch. Internal Med.*, **77**, 385-92 (1946)
166. MITCHELL, G. A. G., *Edinburgh Med. J.*, **54**, 545-60 (1947)
167. DOBRITZ, O., *Z. Urol.*, **40**, 271-80 (1947)
168. PAGE, I. H., AND CORCORAN, A. C., *Experimental Renal Hypertension*, 64 pp. (Charles C Thomas, Springfield, Illinois, 1948)

169. GOLDBLATT, H., *The Renal Origin of Hypertension*, 126 pp. (Charles C Thomas, Springfield, Illinois, 1948)
170. ADDIS, T., *Glomerular Nephritis (Diagnosis and Treatment)*, 338 pp. (Macmillan Co., New York, 1948)
171. DOBBS, R. H., *Lancet*, **252**, 360-63 (1947)
172. DARMADY, E. M., *Brit. J. Surg.*, **34**, 262-71 (1947)
173. HICKS, J. H., *Lancet*, **254**, 287 (1948)
174. JOEKES, A. M., AND BULL, G. M., *Proc. Roy. Soc. Med.*, **41**, 678-80 (1948)
175. ALWALL, N., NORVIIT, L., AND STEINS, A. M., *Lancet*, **254**, 60-62 (1948)
176. MURRAY, G., DELORME, E., AND THOMAS, N., *J. Am. Med. Assoc.*, **137**, 1596-99 (1948)
177. LOCALIO, S. A., CHASSIN, J. L., AND HINTON, J. W., *J. Am. Med. Assoc.*, **137**, 1592-96 (1948)
178. BLOXSOM, A., AND POWELL, N., *J. Pediat.*, **1**, 52-57 (1948)
179. ODEL, H. M., FERRIS, D. O., AND POWER, M. H., *Med. Clinics N. Amer.*, **32**, 989-1076 (1948)
180. MARQUIS, H. H., AND SCHNELL, F. P., *Am. J. Med. Sci.*, **215**, 686-93 (1948)
181. MALUF, M. S. R., *Federation Proc.*, **7**, 77 (1948)
182. LOPEZ, M. B. R., *Obstet y ginec ol. latino-amer.*, **6**, 44-51 (1948)
183. FRIIS, N. P., *Acta Med. Scand.*, Supp. 206, 227-40 (1948)
184. CARGILL, W. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 189-92 (1948)
185. WALKER, A. M., AND OLIVER, J., *Am. J. Physiol.*, **134**, 562-79 (1941)
186. WALKER, A. M., BLOTT, P. A., OLIVER, J., AND MACDOWELL, M. C., *Am. J. Physiol.*, **134**, 580-95 (1941)
187. BRUSH, F. H., *J. Urol.*, **53**, 362-64 (1945)
188. HOGEMAN, O., *Acta Med. Scand.*, Supp. No. 216, 264 (1948)
189. GOLUBEW, W. Z., *Intern. Mschr. Anat. Phys.*, **10**, 541-47 (1893)
190. GEBERG, A., *Intern. Mschr. Anat. Phys.*, **2**, 223-29 (1885)

## CONDUCTION AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM<sup>1</sup>

BY HENRY A. BLAIR

*The University of Rochester School of Medicine and Dentistry  
Departments of Radiation Biology and Physiology  
Rochester, New York*

The object of this review is to outline the present situation with respect to the electrical aspects only of excitation, transmission, and inhibition. Therefore, no reference is made to chemical transmitters or to the systems in which they are considered to be primarily important. Neuromuscular transmission was reviewed recently (1, 6, 29, 46, 83). Bullock (11) has reviewed invertebrate electrophysiology. A lecture by Adrian (2) surveys the nervous system as a whole with particular reference to rhythmic action. Lorente de N6's monograph (55) provides extensive references and a large body of new data on electrical phenomena, particularly the demarcation potential, as a function of environmental conditions.

The views expressed on electrical excitation are those commonly held or implied or readily deducible from existing data. Except in a few details, the postulates for the mechanism of synaptic excitation are essentially those of Brooks & Eccles (10). The attitude on inhibition is at variance on the whole with any existing scheme but exhibits no particular originality with respect to details.

### EXCITATION AND CONDUCTION IN FIBRES

Excitable tissues at rest maintain homogeneously polarized plasma membranes, the electrical sign being positive outside and negative inside.<sup>2</sup> The polarization is a function of the permeability of the membrane, the internal and external chemical concentrations, and the metabolism, all of which are mutually related.<sup>3</sup>

<sup>1</sup> This review covers the period from approximately July, 1947 to June, 1949.

<sup>2</sup> There may be cases in which there are regular resting gradations of polarization giving the cell a polar quality; but if so, they are not relevant to the present discussion.

<sup>3</sup> This subject has been reviewed recently by Eccles (19) and is considered extensively by Lorente de N6 (55). [See also (3, 13, 14, 20, 23, 27, 32, 33, 34, 37, 38, 40, 45, 56, 57, 58, 70, 73, 74, 75, 79 to 82)]

Superimposed on the polarized membrane and closely associated with the polarization is the property of excitability. Activity is induced by disturbing the local equilibrium at some point in the system sufficiently that processes are set up leading to the disappearance or reversal<sup>4</sup> of the local polarization. If the stimulus is electrical, excitation occurs at the region of exit of the charges of positive sign (region of cathode of external stimulator, called cathodal by analogy even if there is no external stimulator). Coincidentally with excitation (depolarization) the permeability (electrical conductivity) at this region is increased (12, 38). The undisturbed region, by means of the electromotive force (e.m.f.) of its still polarized membrane, sets up currents through itself and the depolarized region which, on account of geometrical and physical factors, are greatest at the edge adjacent to the active region and, on account of the sign of the polarization, are cathodal at this region (63, 67). These action currents excite and depolarize the remaining membrane progressively so that activation normally proceeds over the whole cell. After a brief interval, the region initially depolarized regains (or reverses) its polarization spontaneously. This process ordinarily follows depolarization after a constant interval of time (absolutely refractory period) which is relatively independent of fibre size. Consequently, the tendency to repolarize may be regarded as a local property of the membrane system not influenced significantly by geometrical factors. Because the interval of time between depolarization and repolarization is relatively constant in nerve,<sup>5</sup> the actual length of the progressing

<sup>4</sup> Curtis & Cole (15) deduced such reversal from the observation that action potentials were about twice as great as predicted from the resting e.m.f. Hodgkin & Katz (40) have adduced considerable support to a hypothesis to account for this phenomenon; it is that the activated membrane, instead of becoming more permeable generally, becomes permeable especially to sodium so that inward movement of sodium ion gives a polarization positive on the inside. Observations of potential changes consequent to environmental alteration of sodium and potassium are in reasonable agreement with theory (26). Reversal of polarization and simple depolarization are qualitatively the same in relation to the present discussion. It should be noted, however, that there may be a transition region at the forward end of the active region which has lost its "potassium" polarization and has not yet acquired its "sodium" polarization and a similar region at the backward end with the reverse situation.

<sup>5</sup> It is reasonable to assume from existing evidence that this interval (absolutely refractory period) is constant over a whole nerve cell, so that repolarization always follows depolarization at the same speed over the same path. However,

depolarized segment is about in proportion to impulse velocity which in turn is about in proportion to diameter (30, 42). The e.m.f. of this new polarization sets up action currents similar to those producing propagation of excitation initially but, despite this, repolarization proceeds over the path of the previous depolarization. The reason that the membrane can develop and maintain repolarization under the influence of action currents similar to those which caused depolarization is obscure, but it is directly related to the fact that repolarization does not include regaining excitability. On the contrary, the newly repolarized membrane, like the depolarized membrane, is absolutely refractory to stimuli. However, on attaining repolarization or shortly thereafter, the membrane begins to reacquire relative instability (excitability) and, during an interval (the relatively refractory period), the sensitivity to local disturbance and ability to conduct return to their original values.

The membrane e.m.f. does not in general regain its initial value in the abrupt repolarization process which, at a given locus occurs within a small fraction of one msec. in mammalian nerve. Instead, in the most complex case, A and C fibres, for example, it shows at first a small deficiency (negative after-potential) which gives way to a small excess (positive after-potential) which in turn goes through a maximal value and subsides to the normal resting level. B fibres show only positive after-potential (22). Excitability is a function of these changes because the end point of return of sensitivity during the relatively refractory period is directly determined by the membrane e.m.f. at that time, low when it is deficient and high when it is excessive. Thereafter, the threshold varies with the membrane potential until it becomes stabilized. This rule applies generally to after potentials but not generally to altera-

---

this is not true of the ventricles of the heart which tend on the whole to depolarize radially outward and to repolarize radially inward, the part excited last recovering first and vice versa. Therefore, it is conceivable that this interval might be lengthened at some part of the nerve cell such as an ending so that it remained depolarized unusually long or that the interval might be graded near an ending so that repolarization proceeded backward from the ending (52). Schoepfle even assumes that the nerve ending does not depolarize at all (71). Saltatory conduction (41) would presumably give irregular or discontinuous depolarizations along the axon. Lorente de N6 (54) however, concludes that the interval between depolarization and repolarization is similar in axon and soma although the velocity in the soma is relatively slow. This favors assumption of uniformity.

tions of membrane potential induced by environmental changes. Lorente de N6 (55) divides the membrane e.m.f. into fractions in discussing these effects. It is not yet apparent that these fractions are real except insofar as they are phases of a single process.

Since electrical and excitability changes are much more easily measured than chemical, they are better correlated with each other than with ionic concentrations or metabolism. In going through a cycle of activity induced by an electrical stimulus the following relations may be remarked. Application of an electrical stimulus gives rise first of all to a propagated electric wave (electrotonus). This is due to progressive charging from the electrodes outward and inward of the electrical capacities of the tissue membranes along with the changes of distribution of the currents engendered by the potentials established across these capacities. It appears most likely that the plasma membrane is one of the capacities involved. Consequently, its polarization will be increased above resting value in the anodal region and decreased in the cathodal region. The term electrotonus has been used variously to describe the state of altered sensitivity of the tissue consequent to the applied e.m.f. rather than, or in addition to, the potential changes. Consequently it is often assumed that the electrotonic reduction of membrane polarization near the cathode constitutes and is an electrical sign of the local state of excitation. While it is true that with stimuli well below threshold the local state of excitation and the electrotonic potential are proportional in the steady state to the applied e.m.f., and therefore to each other, this is not true for larger stimuli; and there are other reasons for not accepting this identity. For example, it is not at all likely that the excitable membrane is the only one polarized electrotonically; it has not been demonstrated that the kinetics of growth and subsidence of electrotonic potentials are identical with those of local excitatory state; also there is another electrical sign, the local potential (35, 43, 44) which has been more nearly identified with local excitatory state at least in its nearly sufficient stages. The local potential is like cathelectrotonus in that it is partial (or complete local) depolarization of the membrane; but it is unlike it in that it is not detectable with stimuli less than 30 per cent to 40 per cent threshold, that it tends spontaneously to increase with stimuli near threshold, that it actually grows into the impulse at threshold, and that the kinetics of its subsidence following insufficient stimuli

near threshold are quite different (initially much slower) than the disappearance of electrotonus.

While obviously the dissociation of two such closely related phenomena depends on definition, it seems fairly clear that if electrotonic potentials are defined as those which would be expected in a stable physical system, the local potential is different in that it is associated with those changes of physicochemical organization of the plasma membrane which are immediately preliminary to the major events constituting the setting up of the impulse. This is particularly true if local potential, when first observable, is a sign of local response (depolarization) sufficient in intensity but not in extension to spread over the cell.<sup>6</sup> In any event theories (36, 55, 68, 78) of electrotonus are based on derivations from physically stable core conductor models. Discrepancies between theory and measurement of the nerve potentials are ascribed to changes of the system induced by current flow. It is known that there are real or apparent physical changes such as increased resistance in the cathodal area (39), and there are probably physiological changes also. For example, it is unlikely that the intrinsic membrane polarizing mechanism will remain constant (nonreactive) under the influence of current flow. The reason for this expectation is that homogeneous polarization of the cell membrane is presumably the resting equilibrium condition. Accidental local variations from this would cause current to flow. Such currents would signal the existence of inhomogeneity and presumably activate mechanisms to restore uniform polarization. These mechanisms may be related to those concerned with afterpotentials which must be resolved by equilibration of some type. Whether the e.m.f. of low regions tends to be raised or of high regions to be lowered or both is not apparent as this mechanism has not been studied. It is desirable, for clarity, to distinguish such physiological responses from the purely electrophysical aspects of electrotonus, even though there may be certain factors of the one proportional to the other in the steady state.

<sup>6</sup> It has not been determined whether or not the local potential arises from a small area depolarized in the same manner as the depolarized area associated with the propagated response. If it does, it should persist for the duration of the absolute refractory period of the tissue concerned at each locus into which it expands and probably exhibit after potential (see p. 417). If it does not, there is no basis at present for predicting its properties except from observation of its kinetics in the axon.

Another important feature of the membrane polarization in relation to externally applied potentials or its own e.m.f. is that it is not discharged condenserwise by current flow but maintains itself batterywise up to the critical level determined by the threshold of excitability rather than by the energetics of the source of the e.m.f.<sup>7</sup> In fact, when a cell is locally depolarized by injury, the e.m.f. of the intact portion of the membrane maintains current flow at a fairly steady level for many hours providing repetitive excitation does not occur (55). This level may not be as high as that obtaining initially on account of contrary polarizations (electrotonus) set up by the injury currents, or on account of changes at the injured region, or by modifications of the e.m.f. There is no evidence at present, however, that the intrinsic e.m.f. fails significantly in the presence of adequate metabolism (55). Therefore, below the response level, lowering of membrane potential by external sources is probably not by reduction of the intrinsic e.m.f. but by counter polarization. A corollary of these considerations is that in propagation of the impulse the currents at the active edge are not subject to reduction by a failure of energy but persist ordinarily until local excitation occurs. In other words, propagation does not depend on the tissue being sufficiently excitable at each region to respond before some arbitrary time at which the local energy providing the action current runs out. On the contrary, the action current persists until excitation is accomplished or until repolarization occurs in that part of the cell over which the impulse has already passed. It may be noted in this regard that, near the critical level for blocking, transmission may occur or not depending on the interval between depolarization and repolarization [absolute refractory period approximately (67)], as well as on the factors ordinarily considered, such as threshold, membrane e.m.f., and excitability.

The local excitatory state can be described fairly accurately with respect to its kinetics, but the nature of all the processes involved are not well understood.<sup>8</sup> It consists of a local change of

<sup>7</sup> This statement does not necessarily imply that the resting membrane is not polarized and contains only a mechanism for transfer of ions. Presumably, at rest the mechanism maintains a membrane polarization and continues to do so even though conditions are altered to permit the original polarization to discharge. Obviously, the kinetics of this mechanism are quite rapid.

<sup>8</sup> Existing formal theories or analyses of excitation (4, 31, 60, 62, 69) are all deficient in one or more regards but are adequate to make correlations or pre-

condition under the influence of the stimulus which, on reaching a certain value (threshold), sets off or expands into an independent spontaneous process the propagated response. With electrical stimuli, the primary process is very probably polarization of the plasma membrane, but with small electrodes and stimuli not greatly over sufficient at least; local response may always precede the complete response.

If the local excitatory state is not brought to threshold by reason of the insufficiency of the stimulus in strength or duration, it subsides about exponentially from levels not close to the threshold and more slowly initially from levels near threshold. The time constant of subsidence in the exponential case is a function of the area excited (greater with greater area) certainly for muscle and probably with other tissues as well. The rate of subsidence determines chronaxie (rapid subsidence, short chronaxie) as well as the effectiveness of summation of successive subliminal stimuli (latent addition). Therefore, both of these factors depend on the size of the area stimulated. The theory of isochronism of Lapicque (equal chronaxies of cells in a conducting chain) appears to have been of value principally as a stimulus to research (47).

The adequate stimuli probably produce only excitation, but electrical stimuli simultaneously produce excitation and inhibition at the regions of the cathode and anode respectively, excepting those cases in which current enters or leaves through a depolarized region. Excitation and inhibition have similar kinetics, roughly those of charge on a shunted condenser; and they are mutually subtractive when developed in succession sufficiently quickly that the first has not subsided when the second is produced. When opposing currents are applied together, the effect is determined by their difference. These properties suggest strongly that excitation and inhibition are electrical polarizations in the opposite and same senses respectively, as the resting membrane polarization, but they may also involve physical changes and physiological responses consequent to those changes of potential as was indicated above. With alternating current, a single phase must be sufficient in strength and duration or it will not excite at all because successive phases produce opposite effects.

---

dictions with moderate exactness within the spheres to which they are specifically designed to apply. Recent theories by Schoepfle (72) and Ozorio de Almeida (61) have received only limited consideration as yet.

During propagation of the impulse, each of the waves of depolarization and repolarization is monophasic to the cell itself; but each is diphasic to a parallel neighbor in the orders anodal, cathodal and cathodal, anodal, respectively<sup>9</sup> (59). As indicated below, a cell approached normally by the impulse is subjected to somewhat simpler current distribution more nearly diphasic (10, 72).

In some tissues, notably myelinated nerve, electrical currents of long duration (several msec. in nerve) produce to a significant degree another change, accommodation, at the electrodes which may be described as an increase of threshold at the cathode and a decrease at the anode. The rate of subsidence of this process is slower than that of local excitation by one or two orders of magnitude. Its physiological function, if any, is obscure, but it fairly certainly is not a significant factor in axonal conduction because action currents are stimuli too brief to produce significant accommodation. It may be a factor at the soma on account of persistent local potentials, if the soma membrane does accommodate. Accommodation may be related to the slow component of electrotonus (55). On account of accommodation, constant electrical stimuli, unlike the adequate stimuli, do not give rise to repeated responses in all tissues. It should be noted, however, that excitable tissues in general recover polarization and excitability under the action of constant stimuli. In consequence, they are able to respond repetitively to either continuous or discontinuous excitatory agents. The reason they are, as noted above, is that the membrane reorganizes with respect to its resting polarization and to the other properties essential to its continued activity before it regains excitability to make it susceptible again to external influences or to action current. Accommodation is a special case in which threshold may be raised out of reach after one or a few responses. Adaptation of certain end organs is superficially a similar phenomenon.

<sup>9</sup> The usual technique of measuring nerve action potential gives a monophasic record. This is essentially the potential change as viewed from a region of the cell surface as the impulse passes along it. An empirical analysis of the monophasic action potential given recently by Rosenblueth *et al.* (67) is compatible with Hermann's model along with certain assumptions regarding variation of resistance with e.m.f. The effects of action currents on neighboring fibres have been suggested as a mechanism of inhibition by presynaptic interaction (28, 65) which is analogous to a view expressed here (see p. 407).

## SYNAPTIC TRANSMISSION

On reaching a synapse, the afferent impulse, by virtue of its electrical component, produces in the post synaptic cell flow of current of a distribution depending on the geometrical relations. If, for example, the afferent terminal is normal to the surface of the efferent soma, the region of contact of the soma is made anodal and the surrounding region cathodal by the afferent wave of depolarization; and these conditions are reversed by the afferent wave of repolarization. Consequently, if the soma is not fully excited by the first wave, the second wave will annul or reverse such states of excitation as have not subsided between the waves. Since it is generally agreed that synaptic transmission is effected only by many afferent impulses acting upon the soma in concert, this case is the most important. According to existing knowledge of excitation, such additive effects can occur only in the common cathodal field of the afferent action currents, *i.e.*, in regions between endings. Maximal addition of excitatory effects from neighboring groups of afferent endings will occur in the common cathodal field when all the afferent endings are depolarizing together.<sup>10</sup> The most complete interference will occur when approximately one-half, properly distributed, of the afferent impulses to a common field are delayed by about one absolute refractory period of the afferent cell (interval between de- and repolarization) because in this case, the field will be made about equally cathodal and anodal by the simultaneous action of the depolarization waves of the one-half of the impulses and repolarization waves of the other. Such interference will result in no excitation (inhibition). Complete inhibition (failure to excite) probably occurs with much less than complete interference *i.e.*, with less than half the impulses out of step. It is assumed here, of course, that the impulses arriving first are insufficient to excite by themselves. Inhibition (anodal effect)

<sup>10</sup> Eccles (17, 18) adopted the contrary view that the separate cathodal effects under synaptic knobs result in summation. While there is experimental evidence that stimulation of large areas facilitates excitation, there is no evidence that stimulation of multiple separate small areas either does or does not. In the present argument, the only difference between the two views concerns time relations involved in whether the de- or repolarization wave is excitatory. Eccles chooses the latter, and then postulates that the areas exhibiting local potential expand into the all or none response when this occurs. Brooks & Eccles (10) agree, however, that excitation in the common cathodal field may occur in the latent addition of local potential effects and afferent impulse.

in the field might, if sufficiently persistent, be carried over from one volley to the next; but excitation can never have a significant remainder since it is always followed by inhibition.<sup>11</sup> An exception to this is the case in which the local potentials have been developed under the endings on the soma (see p. 414).

The precise nature of the geometrical arrangement at the ending is not a factor affecting the general argument. If excitation at the synapse is electrical and if the afferent ending depolarizes and repolarizes, its action currents through the soma will be phasic and of approximately equal values in the aggregate in opposite directions, and will give rise to corresponding phases of excitation and inhibition. Simple end-on contact, such as that postulated above, is simpler with respect to the number of phases and the time relations than a side-by-side arrangement (see however 71).

Considering for the moment only afferent action currents (detonator action) as the synaptic excitant (5, 16, 49), the scheme just outlined conforms to the commonly accepted views on spatial summation (nearly simultaneous cathodal effects in a common field). Summation at the soma can occur only with impulses arriving with separations less than the duration of the afferent wave of depolarization and the period of persistence of the local excitatory state of the soma, *i.e.*, for a time of the order of one msec. Temporal summation in the whole system is spatial summation at the soma of internuncially delayed or repeated impulses with those of a subsequent afferent volley, and it may occur for as long as branching or repeating chains remain active.

Since the afferent neurons branch to send impulses nearly simultaneously to many post synaptic cells, and since the post synaptic cells receive branches in common from many afferent neurons, when summation becomes sufficient to excite a given cell, it is also sufficient on the average to excite the members of the commonly or similarly innervated group. Therefore, groups of

<sup>11</sup> It should be noted in this regard that latent addition of a postsynaptic cell is not determined only by subsidence of the local excitatory state, but also by the anodal effect of the repolarization wave of the afferent impulse. In other words, synaptic stimulation is analogous to that with alternating current. In consequence measurements of latent addition at the soma, using afferent impulse and direct shock, may not reveal the true rate of subsidence although it will give the effective one. If local potentials occur on the soma, this statement must be modified because in that case latent addition would be determined in large part by the persistence of local potential and of its excitatory effect.

postsynaptic cells respond synchronously and their impulses start out as synchronous volleys. As the afferent inflow is increased in intensity, the synchronous group will expand according to the pattern of common innervation; and with a high level of afferent inflow the whole fraction of a pool with overlapping innervation will tend to fire synchronously. Consequently a synaptic mechanism requiring spatial summation of overlapping innervation converts a random barrage into synchronous volleys. The synchronization of large groups of continuously active cells of higher centers is presumably on this basis rather than isorhythmicity.

Since nearly simultaneous arrival of a minimal number of impulses is a necessary condition for synaptic transmission, it is to be expected that afferent volleys will be the type of inflow most easily transmitted on account of the partial synchronization of arrival of the impulses. While this is no doubt true, it is easily seen that a random inflow if sufficiently intense, will provide sufficient summation at a given moment to cause excitation. Furthermore, once this has occurred, those pre- and postsynaptic elements associated by this transmission will be refractory in order and will become excitable in the same order, so that conditions will be favorable for repetition of the original chain of conduction. As indicated above, other afferent channels becoming synchronous with these will recruit additional elements, while those of the original group which fail to provide impulses sufficiently soon after recovery of the post synaptic cells will allow some to drop out. Impulses arriving out of synchrony will be rejected by refractoriness or by their insufficiency.<sup>12</sup> Consequently, the properties of the synapse make it a selective mechanism rejecting all impulses if they are not sufficiently numerous at a given moment to provide sufficient summation and rejecting that fraction of an effective inflow which does not synchronize with that part which has already established a chain of conduction.

The efficiency of this type of mechanism is functionally dependent on the fibre size (velocity) distributions of afferent nerves (51, 66). If these convey volleys, for example, the postsynaptic

<sup>12</sup> According to Lorente de N6 (53) some channels may be inexcitable for as long as 50 msec. following activity. On the other hand Lloyd (50) has shown that subliminal excitation at the synapse of the two-neuron arc persists in some degree up to 20 msec. Both of these factors are important in complete considerations of synchronization and volleying.

groups excited together will be those innervated by only those afferent bundles whose transmission times are quite similar. It may be of considerable physiological significance that the fibre size distributions are not regular but consist of a few rather narrowly distributed groups.

While the most efficient conduction in a chain will be effected by a system in which equal transmission times carry a volley set up at the first synapse intact to the second and so on, effective conduction can be achieved although wastefully by intersynaptic connections of unequal transmission times, provided they have branches which multiply the number of impulses. The necessity for such multiplication is easily perceived because the synchronous outflow from a synaptic level is much reduced in total number of impulses from random inflow by the selection incident to summation and refractoriness. If this outflow is now randomized, its intensity will be so reduced that it may fail to summate sufficiently at the next level. Consequently a barrage or volley will be blocked within a synaptic chain which does not employ either equal intersynaptic transmission times or intersynaptic multiplication. Since mechanisms for intersynaptic multiplication do exist, random as well as ordered intersynaptic conduction may be postulated.

The question arises as to whether random or ordered arrival may be more advantageous in particular cases. Consider, for example, two independent paths converging at a synaptic level. If each delivered series of separate synchronous volleys, they would arrive by chance alternately or together, sometimes summing, sometimes interfering, a result which is probably undesirable. On the other hand if both arrived asynchronously those impulses which summated at a given time would ordinarily represent contributions proportional to the intensities of activity in their respective paths. This type of integration appears particularly desirable when the converging influences are partly inhibitory and partly excitatory.

In considering cases in which ordered arrival may be advantageous, it appears just as possible for the branches connecting the last two synapses of a conducting chain to have equal as unequal transmission times to produce respectively either a synchronous or asynchronous volley at the final stage. In particular, these branches might equally well be designed to produce two synchronous volleys just sufficiently out of step that the wave of

depolarization of the one and repolarization of the other arrived at the soma simultaneously to give subtractive rather than additive effects. In other words a synaptic mechanism requiring summation for transmission with consequent synchronization of outflow can be employed for the production of either excitation or inhibition at the subsequent stage, the only difference being appropriate inequalities rather than equalities of path lengths leading to that stage from the previous one.

*Inhibition.*—An arrangement for inhibition on this basis may be visualized by considering cells of types A and B differing only in path lengths or transmission times in the last stage before the motor soma. Type A is excited by summation of impulses from a normally excitatory afferent inflow but type B is in the subliminal fringe. Type B also receives impulses of afferent inflow normally inhibitory but is excited only by summation of the excitatory and inhibitory inflows acting together. Thus, if excitatory and inhibitory influences are both active, types A and B are excited in synchrony but their outflows being two interfering volleys at the soma, inhibition is produced. With regard to time relations it will be seen that type B impulses must precede those of A at the motor soma and be normally subliminal; that excitatory and inhibitory volleys arriving at A and B together would produce inhibition at the motor soma; and that an excitatory volley arriving first at A and B would be wholly excitatory at the motor soma if it preceded the inhibitory volley at A and B by the excitation time of A and B. An inhibitory volley arriving first at A and B would be inhibitory at the motor soma if it preceded the excitatory volley at A and B by less than the excitation time of A and B. This mechanism allows the possibility that on occasion with intense excitatory inflow alone, some of type B may be excited to bring about some self inhibition. It also permits the possibility that inhibitory inflow acting alone may on occasion be excitatory because a discharge from B alone would appear the same, qualitatively at least, to the soma as a discharge from A. It may be noted that type A might well be in the subliminal fringe of the inhibitory inflow because this would assist in synchronizing A and B when both excitatory and inhibitory influences were acting together.

It will be seen that excitation and inhibition, according to this scheme, have practically the same properties and time relations. Persistence of inhibition (after discharge) as of excitation for long

periods (greater than the order of 1 msec.) would, of course, be derived from repetitive internuncial chains. This view will be modified presently.

The outline above postulates that inhibition results from asynchrony of a special type—two arrival times properly spaced. If one is committed to the view that synaptic transmission is effective only with a high degree of synchrony (summation), it follows that it would be inefficient with complete asynchrony. Therefore, complete asynchrony might be supposed to provide a type of inhibition, and in the foregoing discussion it might be postulated that the type B cells could be inhibitory in some degree by delivering random impulses to the motor soma. It will be seen, however, that adding random impulses to either a random or synchronous discharge will increase the probability of summation and always lead to increased excitation rather than less (48). Therefore, randomness cannot be used in this way as a mechanism of inhibition, and this is to be expected also because the usual sensory inflow may be random in nature while always excitatory in effect at the first synaptic level.

The mechanism of inhibition in systems involving two-neuron arcs does not fall directly in the scheme proposed above except on the basis of the rather unlikely assumption that requisite transmission time differences can be maintained all the way from the periphery to the motor soma. Inhibition in this case probably requires that the muscle sense afferents send branches to a collateral synaptic level where they unite with endings from inhibitory nerves to produce by another route a synchronous discharge at the motor soma out of step with that of the direct route in the manner of the types A and B cells discussed above. The collateral level will normally be subliminal to excitatory inflow. It may be questioned whether the synaptic level of the collateral branch would be excited in constant appropriate order so that its impulses would arrive at the motor soma in constant relation to the summing impulses of the direct route. It will be seen, however, that since both the motor pool and the collateral level are subjected to the same muscle sense impulses each will be proportionally excited by the same barrage. Therefore, the inhibitory inflow to the collateral from other sensory channels will be facilitated in proportion to the intensity of excitation. It may also be noted that the two-neuron arc afferents form a fairly homogeneous group of large

fast conducting axons. If these are excited abruptly, they will tend to deliver a synchronous volley and once started will tend to repeat such volleys even under constant stretch. This will increase the probability of ordered firing of synapses. With present postulates the inhibitory impulses by way of the collateral should precede the direct flow to the motor soma. This requires that the direct route either be longer by a distance of the order of 1 mm. or possess another property to give equivalent delay.

It has been noted already that summation as a requirement for synaptic transmission accomplishes two potentially useful purposes; first, proportional integration of converging influences, mixed excitation and inhibition being of particular importance, and second, conversion of random inflow to synchronous post-synaptic volleys so that impulse order is obtainable where required. A third attribute of summation which is of prime importance for inhibition is that it permits subliminal inflow. Without this attribute, inhibition would be impossible because, unless the excitatory phases of the action currents of inhibiting nerve endings are subliminal, their inhibitory phases cannot be made to interfere with the excitatory phases of another group.

It is difficult to conceive of great necessity of spatial summation for excitation alone, a one to one correspondence between afferent and efferent impulses being presumably adequate. Consequently, it may be supposed that such complicating features of the nervous system as the summation mechanism and its attendant requirement of branching chains for impulse multiplication, extra synapses for integration, and multiplicity of endings for coordination are specifically designed for inhibition at least in the lower levels of the central nervous system.

Since inhibition is derived primarily from ordered arrival of impulses, it can never result from disorder. Therefore, conditions or agents leading to random spontaneous firing of the central nervous system can result only in generalized excitation. Generalized inhibition is, of course, conceivable as the result of over activity of an inhibitory center with normal conditions prevailing elsewhere. Factors affecting speed of conduction by disturbing relative arrival times will tend to decrease inhibition because, if interference between excitatory and inhibitory phases of action currents is maximal normally, either increase or decrease of transmission times will move the interfering currents out of maximal

opposition. Because order is very dependent on regularity of structure and function, it may be expected that diffuse disease of the nervous system will usually be made manifest first by decrease of inhibition or apparent increase of excitation.

Subnormality and supernormality will have similar effects (decreased inhibition) insofar as they alter interneuronal transmission times. Subnormality, however, may be inhibitory over-all in some degree because greater summation will presumably be required to reach the raised threshold. Gasser (21), in fact, suggested subnormality as a basis for inhibition. Supernormality on the other hand may lead to increase of excitation.

These phenomena may be of special importance when they are not common to the whole system at a given time. For example, if excitatory channels A above have become subnormal through activity while channels B are resting, inhibition suddenly introduced may not attain a steady value until A and B become isosubnormal. Such situations are sufficiently complex, however, that the only conclusion which may be reached at this time is that sub- or supernormality may modify the interplay of excitatory and inhibitory effects.

The discussion up to this point has assumed only rapid synaptic excitation—detonator action—of the type which occurs only during the flow of action current of the afferent ending and which was originally thought to be unique by Lorente de Nó (53). Ordinary excitation of moderate to high levels presumably occurs in this way. The subliminal fringe displays, however, another phenomenon consisting of persistence of excitatory state at the soma for many milliseconds along with relative negativity, the subliminal synaptic potential (10) which is qualitatively similar to the synaptic potential occurring with effective excitation.

Considering now subliminal excitation, or the subliminal fringe of effective excitation, it will be seen that afferent impulses whether excitatory or inhibitory leave the soma field anodal and the regions of the endings cathodal. If these cathodal regions are sufficiently intense to be sites of local potential (partially or wholly depolarized (10, 18), they will be highly negative to the over positive field. Consequently local currents will be set up which are cathodal to the field. These currents will persist as long as the local potential and will render the soma field and dendrite surface cathelectrotonic (partially excited). At the same time the soma and dendrites

will become negative to the axon, as evidenced by the subliminal synaptic potential, which following the impulse will rise rapidly to maximum and then subside as the local areas and the field repolarize. During the synaptic potential phase the soma will be hyperexcitable and will manifest latent addition (facilitation) to new afferent inflow from either inhibitory or excitatory pathways acting alone. It should be noted in this regard that primary inhibition at the soma will facilitate secondary excitation.

If the subliminally excited somata of the subsidiary synaptic level at which inhibition is coordinated have properties similar to those of the motor somata, they will exhibit similar facilitation. Consequently inhibitory inflow will be facilitated in the same way as excitatory, the only difference being the level at which it occurs. The actual mechanism of inhibition at the motor soma will be interference of action potentials as usual. At the coordinating level primary excitation will facilitate secondary inhibition.

If the subliminal fringes of the two levels matched, that is, if only those inhibitory interneurons which were subliminally excited at a given time were those innervating motor somata which also were subliminally excited, it would appear likely that the facilitated inhibitory flow would often be supraliminal at the motor somata and therefore would be excitatory in effect. Actually there is no reason to suppose that such matching will occur except to a degree determined by chance.

Nevertheless, this matched fraction will probably be excitatory at the motor somata at least during the nearly maximal phase of subliminal synaptic potential. Consequently it is to be expected that inhibitory impulses will initially be partly excitatory and partly inhibitory and that inhibition will not be fully developed until this condition has subsided. Experimentally under these conditions inhibition increases from zero at zero interval and is maximal when the conditioning and test volleys are separated by a substantial fraction of one msec. (7, 50, 71). Presumably by this time the motor somata have lost sufficient of their hyperexcitability that the inhibitory impulses have become subliminal and therefore only inhibitory in effect.

Facilitation of excitation does not show any such delay. It is highly developed at zero shock interval because the soma field is cathodal at this time both to the local potentials and to the initial phase of the afferent action current. It should be maximal just be-

fore local potential is maximal, which is slightly later than zero interval, but it will also be maximal at zero interval if the action currents of the endings along with local currents are sufficient to complete excitation at that time. After the initial stages, the overall facilitation of both excitation and inhibition are determined solely by facilitation of excitation at the two synaptic levels concerned and may be expected to be quite similar in persistence. Experimentally, this is found to be so (53).

Lloyd & McIntyre (52) conclude from analysis of the cord potentials recorded from dorsal roots that the negative phase, ascribed to local potentials at the somata by Brooks & Eccles (6) and temporally associated with facilitation, is due instead to persistent depolarization of afferent endings. Despite the evidence adduced this interpretation carries implications, such as depolarization at endings increasing after the impulse, high probability of back-firing in afferent nerves, very long absolutely refractory periods of endings compared to those of axons, and difficulties of conception as to how facilitation is accomplished, which are singularly difficult to accept. Consequently this possibility is not discussed in relation to synaptic processes.

This outline of a mechanism of inhibition on a purely electrical basis is presented for consideration as an alternative to recent hypotheses which employ electrical concepts which are not easily acceptable. It satisfies the demand of observation that inhibition and excitation must have approximately the same properties such as latency, gradation, occlusion, etc. It is fully in accord with the presently established principles of electrical excitation. It requires and therefore accounts for structural complexities such as extra synapses, branching, etc., and physiological complexity such as summation for synaptic transmission, which appear of little necessity for excitation alone or for inhibition on a hormonal basis. It requires no new subsidiary hypotheses of importance excepting that relating to interneuronal transmission times and the collateral synaptic levels for the two-neuron arc systems.

The present hypothesis is similar to the principal existing hypothesis by Brooks & Eccles (6) in the one respect that both require a collateral synaptic level with the two-neuron arc. Those authors employ the neurons of short axons, the Golgi cells for this purpose.

Inhibition is said to be due to anelectrotonus produced under

neuropodia on the motor somata by local potentials of the Golgi cell bodies arising from subliminal excitation. This hypothesis appears to be at variance with accepted views on current distribution and excitation in a number of particulars such as the following,

(a) It is assumed that inhibition is not finally mediated interneuronally by nerve impulses. The theory that axonal transmission of rapid influences is by nerve impulses is so firmly established that it does not seem wise to abandon it without very direct evidence of its insufficiency. However, Gernandt & Granit (24) subscribe to views similar to those of Brooks & Eccles with regard to inhibition in the eye. Another electrotonic hypothesis for inhibition has been presented by Gesell (25). Skogland (76, 77) shows reciprocal effects of stimulating the cord by current in opposite directions which may involve electrotonus as well as more intense cathodes in different regions on current reversal.

(b) It is assumed that Golgi cells are highly excited locally (large local potentials), but do not give all or none responses except on occasion to account for post inhibitory facilitation.

(c) It is assumed that Golgi local currents, although subthreshold to the cell body itself, are able, even when reduced in intensity by the distance of the length of the axon to a value which must be a trivial fraction of threshold, to produce an inhibitory effect in the motor soma sufficient to render ineffective an excitatory effect of superthreshold value. What this assumption means in effect is that opposing currents, differing by one or more orders of magnitude, effectively counteract each other even when they are not superimposed. As a matter of fact, distributed anodal regions among cathodal might, as was indicated above, be excitatory in effect under the conditions postulated.

(d) If Golgi cells are ever excited completely so as to become excitatory to the motor soma, this should occur when the inhibitory inflow is high. It is implied, therefore in this hypothesis that intense inhibitory inflow would always be excitatory, which is not true.

The mechanism suggested here does not account for inhibition of antidromic excitation of the motoneurons by inhibitory inflow (8, 64, 65), for which an explanation is given by Brooks & Eccles on their hypothesis (9). The present scheme predicts in fact that inhibitory inflow acting alone should facilitate the antidromic response just as does excitatory inflow (54). There are other possible

explanations, however, without resorting to inhibitory substances or action at a distance. For example, if local response is the same in character as all or none, it should be followed by local positive after potential under the neuropodia. These depressed areas would act in the same way as the analectrotonic areas postulated by Brooks & Eccles. The time of onset of this inhibition, past the maximum of local potential (several milliseconds after the inhibitory volley) is in keeping with such an explanation. Accommodation of the soma to the currents arising from its local potential may occur as the basis for an alternative or additional explanation.

## LITERATURE CITED

1. ACHESON, G. H., *Federation Proc.*, **7**, 447-57 (1948)
2. ADRIAN, E. D., *Brain*, **70**, 1-17 (1947)
3. ALBRINK, W. S., AND FUOSS, R. M., *J. Gen. Physiol.*, **32**, 445-53 (1949)
4. BLAIR, H. A., *Biol. Symposia*, **3**, 51-93 (1941)
5. BREMER, F., *Ann. physiol. physicochim. biol.*, **9**, 897-900 (1933)
6. BROOKS, C. MCC., AND ECCLES, J. C., *J. Neurophysiol.*, **10**, 251-73 (1947)
7. BROOKS, C. MCC., AND ECCLES, J. C., *J. Neurophysiol.*, **11**, 401-16 (1948)
8. BROOKS, C. MCC., ECCLES, J. C., AND MALCOLM, J. L., *J. Neurophysiol.*, **11**, 417-30 (1948)
9. BROOKS, C. MCC., AND ECCLES, J. C., *J. Neurophysiol.*, **11**, 431-44 (1948)
10. BROOKS, C. MCC., AND ECCLES, J. C., *J. Neurophysiol.*, **11**, 365-76 (1948)
11. BULLOCK, T. H., *Physiol. Revs.*, **27**, 643-64 (1947)
12. COLE, K. S., AND CURTIS, H. J., *J. Gen. Physiol.*, **22**, 649-70 (1939)
13. CRESCITELLI, F., *Am. J. Physiol.*, **155**, 82-91 (1948)
14. CRESCITELLI, F., *J. Cell. comp. Physiol.*, **32**, 187-210 (1948)
15. CURTIS, H. J., AND COLE, K. S., *J. Cellular Comp. Physiol.*, **19**, 135-44 (1942)
16. ECCLES, J. C., *J. Physiol. (London)*, **91**, 1-22 (1937)
17. ECCLES, J. C., *Nature*, **156**, 680-82 (1945)
18. ECCLES, J. C., *Ann. N. Y. Acad. Sci.*, **47**, 429-55 (1946)
19. ECCLES, J. C., *Ann. Rev. Physiol.*, **10**, 93-116 (1948)
20. FELD, E. A., GRUNDFEST, H., NACHMANSOHN, D., AND ROTHENBERG, M. A., *J. Neurophysiol.*, **11**, 125-32 (1948)
21. GASSER, H. S., *Harvey Lectures*, **32**, 169-93 (1937)
22. GASSER, H. S., *Ohio J. Sci.*, **41**, 145-59 (1941)
23. GALLEGO, A., AND LORENTE DE NÓ, R., *J. Cellular Comp. Physiol.*, **29**, 189-206 (1947)
24. GERLANDT, B., AND GRANIT, R., *J. Neurophysiol.*, **10**, 295-301 (1947)
25. GESELL, R., HANSEN, E. T., AND SISKEL, J., *Am. J. Physiol.*, **148**, 515-29 (1947)
26. GOLDMAN, D. E., *J. Gen. Physiol.*, **27**, 37-60 (1943)
27. GRAHAM, H. T., AND BLAIR, H. A., *J. Gen. Physiol.*, **30**, 493-517 (1947)
28. GRUNDFEST, H., *Ann. Rev. Physiol.*, **2**, 213-42 (1940)
29. HARVEY, A. M., *Federation Proc.*, **7**, 458-63 (1948)

30. HERTZ, H., *Acta Physiol. Scand.*, Supp. 43, 13, 1-91 (1947)
31. HILL, A. V., *Proc. Roy. Soc. London [B]*, 119, 305-55 (1936)
32. HILL, D. K., AND KEYNES, R. D., *J. Physiol. (London)*, 108, 278-81 (1949)
33. HÖBER, R., *J. Gen. Physiol.*, 30, 389-97 (1947)
34. HÖBER, R., LANGSTON, M., STRAUSSER, H., AND MACEY, R., *J. Gen. Physiol.*, 32, 111-20 (1948)
35. HODGKIN, A. L., *J. Physiol. (London)*, 91, 5P-7P (1937)
36. HODGKIN, A. L., AND RUSHTON, W. A. H., *Proc. Roy. Soc. London*, [B]133, 444-79 (1946)
37. HODGKIN, A. L., *J. Physiol. (London)*, 106, 316-40 (1947)
38. HODGKIN, A. L., AND HUXLEY, A. F., *J. Physiol. (London)*, 106, 341-67 (1947)
39. HODGKIN, A. L., *J. Physiol. (London)*, 106, 305-18 (1947)
40. HODGKIN, A. F., AND KATZ, B., *J. Physiol. (London)*, 108, 37-77 (1949)
41. HODGKIN, A. F., AND STÄMPFLI, R., *J. Physiol. (London)*, 108, 315-39 (1949)
42. HURSH, J. B., *Am. J. Physiol.*, 127, 131-39 (1939)
43. KATZ, B., *Proc. Roy. Soc. London*, [B]124, 244-76 (1937)
44. KATZ, B., *J. Physiol. (London)*, 106, 66-79 (1947)
45. KATZ, B., *J. Physiol. (London)*, 106, 411-17 (1947)
46. KUFFLER, S. W., *Federation Proc.*, 7, 437-46 (1948)
47. LAPICQUE, L., *Arch. Néerland. physiol.*, 28, 377-84 (1948)
48. LLOYD, D. P. C., *Howell's Textbook of Physiology*, 165-71 (J. F. Fulton, Ed., W. B. Saunders Co., Philadelphia, Pa., 1946)
49. LLOYD, D. P. C., *J. Neurophysiol.*, 9, 419-38 (1946)
50. LLOYD, D. P. C., *J. Neurophysiol.*, 9, 439-44 (1946)
51. LLOYD, D. P. C., AND CHANG, H.-T., *J. Neurophysiol.*, 11, 199-208 (1948)
52. LLOYD, D. P. C., AND MCINTYRE, A. K., *J. Gen. Physiol.*, 32, 409-44 (1949)
53. LORENTE DE NÓ, R., *J. Neurophysiol.*, 2, 402-64 (1939)
54. LORENTE DE NÓ, R., *J. Cellular Comp. Physiol.*, 29, 207-87 (1947)
55. LORENTE DE NÓ, R., *A Study of Nerve Physiology*, 131, 132, 496 pp., 548 pp. (Rockefeller Inst. Med. Res., New York, 1947)
56. LORENTE DE NÓ, R., *J. Cellular Comp. Physiol. Supp.*, 33, 1-231 (1949)
57. LUNDBERG, A., *Acta Physiol. Scand.*, Supp. 50, 15, 6-65 (1948)
58. LUNDBERG, A., *Acta Physiol. Scand.*, Supp. 53, 16, 43 (1948)
59. MARRAZZI, A. S., AND LORENTE DE NÓ, R., *J. Neurophysiol.*, 7, 83-101 (1944)
60. MONNIER, A. M., *L'excitation électrique des tissus*, 326 pp. (Hermann & Cie, Paris, 1934)
61. OZORIO DE ALMEIDA, M., *Anais. acad. brasil. cienc.*, 19, 165-76, 177-87 (1947)
62. RASHEVSKY, N., *Protoplasma*, 20, 42-56 (1933)
63. RASHEVSKY, N., *Physics*, 4, 341-49 (1933)
64. RENSHAW, B., *J. Neurophysiol.*, 5, 235-43 (1942)
65. RENSHAW, B., *Am. J. Physiol.*, 146, 443-48 (1946)
66. REXED, B., AND THERMAN, P. O., *J. Neurophysiol.*, 11, 133-40 (1948)
67. ROSENBLUETH, A., WIENER, N., PITTS, W., AND GARCÍA RAMOS, J., *J. Cellular Comp. Physiol.*, 32, 275-318 (1948)
68. ROSENBERG, H., *Proc. Roy. Soc. London [B]*124, 308-36 (1937)
69. RUSHTON, W. A. H., *Proc. Roy. Soc. London [B]*124, 210-43 (1937)
70. SALISBURY, P. F., *J. Cellular Comp. Physiol.*, 29, 345-55 (1947)
71. SCHOEFFLE, G. M., *J. Neurophysiol.*, 10, 339-47 (1947)

- 72. SCHOEFFLE, G. M., *J. Neurophysiol.*, **11**, 509-18 (1948)
- 73. SHANES, A. M., *J. Cellular Comp. Physiol.*, **27**, 115-18 (1946)
- 74. SHANES, A. M., AND HOPKINS, H. S., *J. Neurophysiol.*, **11**, 331-42 (1948)
- 75. SHANES, A. M., *Am. J. Physiol.*, **153**, 93-108 (1948)
- 76. SKOGLAND, C. R., *Acta Physiol. Scand.*, Supp. 47, **14**, 1-16 (1947)
- 77. SKOGLAND, C. R., *Acta Physiol. Scand.*, Supp. 47, **14**, 1-13 (1947)
- 78. STOHL, A., AND MARTIN-BELLET, F., *J. physiol.*, **39**, 35-47 (1946-47)
- 79. TASAKI, I., AND FUJITA, M., *J. Neurophysiol.*, **11**, 311-16 (1948)
- 80. TEORELL, T., *Acta Physiol. Scand.*, Supp. 53, **16**, 62-3 (1948)
- 81. TOMAN, J. E. P., WOODBURY, J. W., AND WOODBURY, L. A., *J. Neurophysiol.*, **10**, 429-41 (1947)
- 82. USSING, H. H., *Physiol. Revs.*, **29**, 127-55 (1949)
- 83. WELSH, J. H., *Federation Proc.*, **7**, 435-36 (1948)

## SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM<sup>1</sup>

BY ARTHUR A. WARD, JR.

*Division of Neurosurgery, University of Washington School of Medicine  
Seattle, Washington*

"It is indeed remarkable how much of the physical world, amid the conflicting action of a great variety of unconnected forces, can be described by the simplest mathematical function,  $x^n$  and  $e^x$ ." (1).

### CYBERNETICS

The evolution of knowledge regarding the central nervous system has now reached a stage where it is slowly becoming possible to apply methodologies novel to this field. Although the hope quoted above can unfortunately (or fortunately) not yet be applied, we have seen the birth of a new word "Cybernetics" (from the Greek word for steersman), which has been introduced to encompass the entire field of control and communication theory of which the nervous system is an example.

As Rosenblueth & Wiener (2) pointed out five years ago, scientific knowledge consists of a sequence of abstract models, preferably formal, occasionally material in nature. The material models start by being rough approximations of the original situation and asymptotically approach the complexity of the original situation. As a limit, it will become that system itself. Thus the only completely satisfactory map to scale of a given country will be that country itself. This is the process of abstraction, which consists in replacing the part of the universe under consideration by a model of similar but simpler structure. Models, formal or intellectual on the one hand, and material on the other, are thus a central necessity of scientific procedure.

Wiener (3), in his book introducing the science of Cybernetics, points out that many automata (automatic gyro-compass, self-propelled missiles, and rapid computing machines, etc.) are coupled to the outside world both for the reception of impressions and for the performance of actions. They possess sense organs, effectors, and the equivalent of a nervous system to integrate the transfer of information from the one to the other. Thus they can be subsumed

<sup>1</sup> This review covers the period from July, 1948 to July, 1949.

under one theory with the mechanisms of physiology. This newer study of automata, whether in the metal or in the flesh, is a branch of communication engineering; and its notions are those of message, quantity of information, amount of disturbance or "noise" feedback and oscillation, etc. In approaching these problems, the theory belongs to the Gibbsian statistical mechanics rather than to the classical Newtonian mechanics in which so much neurophysiology has been stated in the past, and it is here that the major break with the old physiology occurs. This approach requires new concepts and a new language, as well as intercourse between minds specialized in nonbiological fields. One example of this is embodied in a symposium entitled "Teleological Mechanisms" (4).

The rapid advances in the theory and construction of computing machines (5) and the close analogies between them and the central nervous system (3, 6, 7) have made possible machines, such as that constructed by Ashby (8), designed to copy the essential features of any given circuit so that it will show by its behavior how such a system would behave. One can in this way study the effects of various types of feedback, whether simple, multiple, or more particularly, patterned in some complex way. He has been able to show that two dynamic systems, each intrinsically stable, may become unstable when joined; that joining units can only decrease stability; and that if part of a stable system is slowed down, the whole may become unstable. These may offer a clue to the intrinsic potential instability of the primate nervous system and the means by which gross instability (e.g., Parkinsonian tremor) may be precipitated in such systems.

At the formal level, McCulloch & Pitts (9, 10, 11) have applied certain tools of statistical mechanics to central nervous system problems, and thereby described the actions of neurons and their mutual relations by the calculus of propositions subscribed for time. It has been possible to state the way in which the nervous system may detect universals; how it adjusts the all-or-none laws governing its elements to a physical world of continuous variations; how it chooses between ends; and how it alters its structure by experience. The "probabilistic" rather than the previous "deterministic" approach to the theory of neural nets has been continued by Shimbel and others (12, 13, 14). Culbertson (15), in a similar fashion, has described a mechanism for the recognition of visual form and for bottle-neck optic nerve conduction.

As further examples of this approach, an empirical, rigorous mathematical description of the monophasic spike potential has been developed by Rosenblueth *et al.* (16). A study of the cochlea by Gold & Pumprey (17) has shown that this organ acts as a frequency analyzer. As he points out, because of the slow rate of central nervous system action, information must be lost unless a transformation occurs at the receptor. The pressure-time variation must be coded so that each fiber carries only an assigned fraction of information. The tympanic organ of insects signals the mean acoustic power which it absorbs in successive short intervals of time. Many channels are then necessary for intensity discrimination over a wide range of intensities. In mammalian ears, the problem of accepting items of information more rapidly is solved by the device of frequency analysis, in which the peripheral analyzer is such that the selectivity of the resonant elements is proportional to frequency. The ear is a perfect analyzer to a frequency of one kilocycle per second. Above that it is imperfect, not because of inadequate selectivity, but because perfection would require an impracticable number of resonant elements and nerve cells. Gold (18) has shown that the cochlea itself has a local feedback mechanism which functions as a linear amplifying device and hence, not possessing any threshold, makes a construction possible where the nerve ends abstract much energy from the mechanical resonator. Under these circumstances, the sensitivity is no longer limited by the thermal agitation of the nerve fiber, but by that of the resonator; and as the latter is a tuned element and the former is not, the two limits will be substantially different. On this basis, the phenomenon of ringing in the ears may be due to a spontaneous oscillation of the local feedback, and the theory may also explain the often observed apparent change of pitch with intensity.

With regard to somatic sensation, Walter & Walter (19) have indicated that, in general, differences in stimulus intensity are converted into differences in impulse frequency, i.e., receptors operate a system of pulse frequency modulation. Secondly, peripheral transmission is such that changes in stimulus intensity are transmitted rather than steady or absolute levels. This corresponds to a process of differentiation whereby rapid changes produce a greater effect than slow ones, thereby achieving a high sensitivity without blocking by high steady intensities (cf. differential coupling in amplifiers, etc.). They have also discussed in some detail some of the distortions inherent in such a system and how illusions

would occur in the central nervous system in association with appropriate rhythmic stimulation.

Thus a new approach to central nervous system problems is under way. Experimental verification in simple systems is in progress, but the application to more general phenomena, such as biological rhythms of long period (20), has not been possible as yet. New experimental methods, such as establishing the correlation between the electrical activity of various portions of the nervous system (21) or electronically mapping the activity of the heart and brain (22), will give additional information.

#### CEREBRAL CORTEX

It is probable that the brain functions both as an analogue and a digital computing machine, but the details by which this is accomplished, as well as an analysis of the complicated servomechanisms enabling us to act with facility and precision, are not possible until further information is available. Only relatively crude data exists regarding the "wiring" of the brain, and a portion of this is summarized in *The Precentral Motor Cortex* (23), a new edition of which has recently appeared. The introduction of a more precise method for studying fiber degeneration by the intravenous methylene blue technique (24) may yield further information regarding interconnections within the brain which are at present unknown.

The method of physiological neuronography has yielded further data regarding the corticocortical connections of the superior bank of the Sylvian fissure (25), of the cortex lying within the arcuate and lunate sulci (26), and of the superior surface of the temporal operculum in the monkey (27). By anatomical techniques, the distribution of the anterior commissure has been studied in detail (28, 29) and found to project to the middle temporal gyrus via its posterior limb with a smaller projection over the anterior limb to the olfactory tubercle, anterior olfactory nucleus, and olfactory bulb. The connections of the triangular gyrus in primates have also received attention (30). The cortical projection of proprioception has been reported (31), but the method employed is not entirely convincing.

The localization for vocalization and arrest of speech in the human have been described (32), as well as disorders of the body

image caused by lesions of the parietal lobe (33). Ades & Raab (34) have reported the effect of preoccipital and temporal decortication on learned visual discrimination. They conclude that the loss of the form-discrimination habit represents a specific perceptual deficit. Furthermore, on the basis of serial removals, they postulate that injury to a part of the neural apparatus utilized in a given integration, sets off a process of functional reorganization which has reverberations beyond the confines even of the hemisphere in which it begins, such that, when a second operation demolishes the residue of formerly critical tissue, it has somehow ceased to be critical and the learned habit is not disrupted. This problem of functional reorganization or "learning" is of fundamental importance, and few of the intimate details are known. Sperry (35) has shown that when a transplanted eye is rotated 180 degrees, the recovered visuomotor responses show a directional reversal which is directly correlated with the rotated position of the eye. Since this is obviously maladaptive, it would lend support to a theory of biochemical affinity regarding the developmental organization of synaptic connections. The regeneration of fibers within the central nervous system and the re-establishment of functional connections are also not due to mechanical guidance or adaptation by function (36). However, it is not entirely clear what relation these findings have to the modification of synaptic function which is postulated to occur in learning. That mechanical factors alone are not of prime importance in all aspects of neuronal growth is further indicated by the fact that fissure formation in the brain will occur in the absence of thalamocortical projections, corpus callosum, and even after removal of large parts of the fetal hemisphere. In fact, fissure formation will occur in pieces of cortex attached only by a vascular fold (37).

*Motor system.*—Denny-Brown & Botterell (38) have reviewed the function of the precentral gyrus in the higher primates, and Mettler (39) has discussed certain nonpyramidal functions of this region. Careful mapping of the motor cortex by stimulation has been reported for the marmoset (40), the dog (41), and the rat (42). Movements of the head and eyes as the result of cortical stimulation in the human have been summarized by Rasmussen & Penfield (43), who point out that one third of these points are located immediately anterior to the central sulcus while the re-

maintaining two thirds of the loci are situated in the anterior half of the precentral gyrus or in the caudal portion of the adjacent frontal convolutions. Obviously the eye-turning area in the human is more closely related to the sensorimotor region than the results of stimulation of the cortex of other primates would suggest.

Among the many factors which influence the response to stimulation of the motor cortex, Gellhorn (44, 45) has studied the influence of the proprioceptive inflow. Such proprioceptive impulses can modify the response of a given focus quantitatively, but not qualitatively. Thus an increase in initial muscle length will cause an increased response to cortical stimulation, as well as an increase in the response of synergistic muscles with increased inhibition of the antagonists. He was unable to produce a reversal of the type of movement by these means, however. With fixed cortical stimulation in the unanesthetized monkey, it is also true that the stability of a cortical point is maintained only so long as the initial position of the limb is maintained (46). Under these conditions, it is also impossible to distinguish between responses from area 4 and area 6 on the basis of threshold or character of response.

The anatomical features of the pyramidal tract have been rather completely discussed by Lassek (47) and Verhaart (48), while Woolsey & Chang (49) have shown that antidromic pyramidal tract potentials can be recorded from a rather wide area of cortex, including areas 8, 6, 4, 3, 1, 2, 5, and 7 in the monkey. The same technique has been applied to a study of the corticospinal tract from the bulbar pyramid down into the cord (50). By means of his degeneration method, Glees & Cole (51) have found that small lesions in the hand area result in degeneration which extends down the pyramidal tract, not only into cervical levels, but down to the lumbar region. On this basis, they postulate that the reappearance of a motor pattern after area 4 lesions may be explained by these plurisegmental connections. Because of the technical surgical difficulties inherent in the production of lesions confined strictly to one subdivision of area 4, further confirmation of these results is awaited.

All these and past studies of the motor cortex have been concerned, in greater or lesser degree, with what is known as the "problem" of localization. This problem is still a cause of concern (52, 53) and has led Clark (54) to discuss the matter in some de-

tail. He points out that any particular group of spinal internuncials receives many, and perhaps a majority, of its corticospinal fibers from one small area of the cortex. In addition, fibers from other portions of the motor cortex will affect the same group, but the number from each unit decreases steadily as the distance from the primary focus increases. Thus threshold stimulation of the motor cortex would excite only those cells which are in the proper stage of facilitation. These impulses, in turn, pass to the spinal internuncials, but the particular internuncials fired would be determined by concurrent activity there. This activity could come from intraspinal afferents, vestibular fibers, facilitatory and suppressor systems of the bulbar reticular system, etc. This concurrent activity is in accordance with Lorente de Nó's "optional transmission circuits" which summate with corticospinal activity to produce reversals in response, etc., which account for the variations described by many workers. In other words, the response to cortical stimulation is not determined solely by the point stimulated; and final integration is not accomplished at the cortical level. This statement is certainly in agreement with all recent work in the field. However, it is becoming increasingly clear that the use of such terms as punctate, multiple muscle, or the search for rigid localization with reference to the function of the motor cortex is largely meaningless. Localization in this sense does not exist in any system operating under the principles of statistical mechanics.

Penfield (55) has pointed out that the precentral gyrus is essential to the performance of the skilled movement acquired later in life, and yet there is no change in the result of electrical stimulation before and after the acquisition of skills. Likewise, there is no evidence that the epileptic discharge is capable of activating acquired neurone connections. Memory need not be lodged in any one locus in the machine, but belongs to its function as a whole (7); and the same is evidently true of the brain (55). Thus, since nervous activity is never (at least in the brain) immutable, the search for localization in terms of Newtonian mechanics is not justified.

*Frontal lobes.*—This question of localization becomes even more acute with regard to function of the frontal lobes. It is increasingly clear that specificity of frontal lobe function in the human has yet to be demonstrated (56, 57). Relatively discrete

ablation or undercutting of specific portions of the human frontal lobe (56, 58 to 64) have now been carried out, and the early results indicate that the social consequences or the effects on personality are related less to locus of damage than to the number of neuronal circuits interrupted. On the basis of our inadequate knowledge of the wiring of this part of the brain and the rough predictions from communication theory, this should not be too surprising. It is probable that the search for structures more directly implicated in restricted subphenomena of this category, which is the ultimate goal of psychosurgery (65), should be directed elsewhere than in the frontal association areas.

Attempts continue to be made to analyze the functions of the frontal lobes (66, 67, 68) from which additional information is gained, and this is supplemented by continuing investigation of this problem in primates (69, 70, 71). A sound background of information regarding the construction and connections of the frontal lobe is being accumulated. The cytoarchitecture of the frontal lobe has been described recently in the primates (72) and in the chimpanzee and man (73), as well as a careful study of cortical areas 13 and 14 in the human (74). McCulloch (75) has summarized present knowledge concerning the connections of the frontal lobe as established by physiological neuronography, and anatomical evidence concerning the projection systems from this region has also been presented (76, 77).

The projection of the mediodorsal nucleus to the orbitofrontal cortex has been carefully studied in the rabbit, sheep, and cat by Rose & Woolsey (78). In man, Freeman & Watts (79) describe the thalamofrontal projections in some detail, stating that the lateral and central portions of the dorsomedial nucleus project to areas 9 and 10, while the medial part of that nucleus projects to the base. Hassler (80) is not in entire agreement, stating that the two anterior regions of the dorsomedial nucleus project to the orbital and the two middle regions of that nucleus project to areas, 9, 44, and 45.

Evidence is accumulating that certain nonsomatic efferent functions are associated with activity of restricted portions of the frontal lobe. Stimulation of the posteromedial portion of the orbital surface in the monkey (81) causes vascular, respiratory, and gastrointestinal responses which may be independent of each other. The vascular responses consist either of an instantaneous

fall or a slow rise in blood pressure, and the authors quote Cort (144) who is said to have shown that similar stimulation in the cat evoked a shunting of blood flow within the kidney with a consequent renal cortical ischemia and anuria. Respiration is arrested in expiration. Excision of this region causes marked general hyperactivity. The respiratory and vascular responses from orbital stimulation have been confirmed in the human (82, 83). Respiratory arrest can be elicited also from the region of the sulcus principalis in the monkey (84) and from a wide band extending from the temporal pole, anterior insula, posterior orbital surface, the subcallosal region and onto the rostral limbic gyrus (85). This zone also includes the uncus, limen insulae, and anterior perforated space. It is also possible that the cardiovascular responses may be obtained from stimulation of the lateral convexity of the frontal lobe (86).

Shenkin *et al.* (87) have shown that frontal lobotomy in the human produces a reduction in cerebral blood flow and oxygen consumption, while Reed (88) describes an increased gastric acidity. Sweet *et al.* (89) have described the case of one patient in detail in whom bilateral frontal lobotomy was followed by a massive hemorrhage into the gastrointestinal tract, azotemia and subsequent hyperglycemia, hyperchloremia, and hypernatremia. Post-operative azotemia and hyperchloremia were present in three additional cases with damage in this region. Lastly, Reitman (90) has reported a uniform diminution in 17-ketosteroid excretion following lobotomy. Thus, mechanisms exist in the frontal lobe which are intimately concerned with the maintenance of the internal environment of the organism, although the details of the circuits involved are entirely unknown.

*Limbic lobe.*—Increasing interest is being shown in this system which may prove to be of even greater clinical importance than the frontal lobe. Although the gross connections of area 24 (anterior limbic region) are known, Gardner & Fox (91) have studied the distribution of the cingulum in detail and find that there is only a slight projection forwards. The major projection is occipitalwards, a few fibers passing to areas 19 and 18, with the bulk curving retrosplenially into the pyriform lobe and probably to the hippocampus. Continuing his study of the functions of the limbic cortex, Smith (92) has reported the results of stimulation of the posterior pyriform area. Activation of this region evokes

risers in bladder pressure, as well as vocalization and cardiovascular effects quite similar to those obtained from the anterior limbic area, although the cytoarchitecture of these two regions is vastly different. Rose & Woolsey (93) have described the cytoarchitecture of both the anterior and posterior limbic regions and have shown that the anteromedial nucleus of the thalamus projects to the anterior limbic region, the anteroventral to the cingular field, and the anterodorsal to the retrosplenial area. The essential unity of the entire limbic lobe is further indicated by the fact that respiratory and vascular responses can be obtained from a large portion of it (85). A brief description of the nuclei of the amygdaloid nucleus and its fiber systems has appeared (94), as well as a description of fiber degeneration in Ammon's horn from lesions of the pyriform and other cortical areas (95).

Although it is not clear exactly what role the entire limbic lobe plays, theories of its function are brought forward (96). Based on the evidence that lesions of area 24 in the monkey result in certain changes in personality, this procedure has been carried out in the human by Ward (65); but too little is known to evaluate what part this specific area plays in the elaboration of personality in the human. However, Bard & Mountcastle (97) have shown that the limbic lobe is essential to certain emotional responses in lower forms. Whereas bilateral removal of the greater part of the telencephalon in the cat causes it to show anger on slight provocation, bilateral removal of neocortex with preservation of rhinencephalic structures results in an animal remarkable for its extreme placidity. Further evidence that activation of this general system may cause bizarre social activity in the human comes from observations on patients with epileptogenic foci in the temporal lobe, especially over its tip (98, 99). Thus, it is quite possible that certain circuits of this system are closely associated with emotional response and its study in relation to personality disorders in the human is further indicated.

*Suppression.*—A certain confusion seems to exist regarding the phenomenon of suppression and the relation between it (as described by Dusser de Barenne *et al.*) and spreading depression (as described by Leao). Suppression of both electrical and motor activity can be obtained by the topical application of physostigmine and acetylcholine (100), and suppression has again been described in the human (101). However, Clark & Ward (46), while

studying the effect of cortical stimulation in the unanesthetized monkey, have never observed anything resembling it. Stimulation of area 24 under these conditions brings the animal to a halt for the duration of the stimulus, with one foreleg poised off the table. These authors did obtain muscular relaxation with stimuli under threshold values, which they felt could not be confused with suppression.

The spreading depression of Leao has been studied in some detail (102, 103), and, although it is easily elicitable in the rabbit, it can only be demonstrated in the cat occasionally. In the former, it is certain that spreading depression affects only the purely cortical events and no subcortical or intracortical block of afferent impulses occurs. The relationship between these phenomena and the inhibition obtained from the brain stem and that which occurs in the cord are also not clear.

*Epileptic seizures.*—Ward, McCulloch & Kopeloff (104) have shown that the experimental cortical scar differs from the rest of the cortex as indicated by the random fluctuations of its noble metal potential, but not by its pH. The electrical seizures arising from such a focus have been studied and their mechanism and type of spread through the brain described. These findings have been further elaborated (105, 106) especially with regard to the local electrical changes and the sign of the potential, as well as the effect of thalamocortical systems on the type of electrical discharge with special reference to the petit mal type of disturbance due to rhythmic stimulation of the intralaminar system of the thalamus (107). Certain differences between cortically and subcortically induced convulsions have been reported (108, 109), and also the role of afferent impulses as precipitating factors in producing seizures (110). Occasional dramatic instances of this are also seen in the human (111). The potentiating action of physostigmine, prostigmine, and mecholyl on seizures is accompanied by the report that diisopropylfluorophosphate has no such effect (112).

Evidence has also been presented regarding the chemical milieu as a factor in the spread of the epileptic discharge (113) and the action of carbon dioxide on epileptic activity (114, 115, 116). Certain biochemical studies (117) indicate that the epileptic brain shows no difference in rates of aerobic or anaerobic glycolysis. On this basis, it is probable that the epileptogenic brain contains normal neurons which are subjected to abnormal stimuli. This is

also intimated by the fact that the epileptogenic focus is more prone to afterdischarge (118). The neuropharmacology of anti-epileptic drugs is being studied (119), and Torda & Wolff (120) state that the activity of carbonic anhydrase is inhibited by convulsant agents in low concentrations and increased by anticonvulsants.

*Electrical activity of brain.*—Many problems remain to be solved regarding the origin and nature of the electrical disturbances recorded from the scalp or directly from the cortex (7, 121, 122). The effect of sleep, body temperature, cord section, age, and drugs on these rhythms have been studied (122 to 127). It is definite that certain cortical fields show a distinctive electrical discharge (128), which is in part determined by the particular thalamocortical reverberating circuits involved (125). In this regard, it is now known that the ascending pathway of the corticothalamic reverberating circuit does not use fibers mediating the great afferent volleys (129).

One method of investigating an electronic circuit whose parts cannot be individually studied, is to impose known frequencies on its input, and, by then studying the output, determine in what way the apparatus modifies the known signals. This technique has proved exceedingly valuable in the field of electroencephalography (19, 130 to 133). As additional information of this kind accumulates, it may become possible to treat the data on a rigid statistical basis.

#### DIENCEPHALON

*Thalamus.*—Now that this portion of the brain is accessible to neurosurgical attack in the human (134, 135), an added impetus has been given to the study of its functions. Information is available regarding the afferent input and the cortical projection of the main sensory nuclei. Most of the thalamic nuclei are now thought to have a cortical projection, in certain mammals at least, but no such connections have been demonstrated for the paratenialis, rhomboidalis, or nucleus subthalamicus in the rat (136). Although the centre median apparently does project to the cortex in this animal, in the human such connections are limited to the striatum with none to the globus pallidus (137). An interthalamic commissure is present between the lateral thalamic nuclei (138), and more information of local interconnections is needed. The dis-

crete pattern of tactile representation in the thalamus has now been worked out (139, 140), including the thalamic relay for the second somatic sensory receiving area (141). The study of reverberating circuits between thalamus and cortex continues and is supplemented by simultaneous recording of thalamic and cortical potentials in the human (142) and observing the effect of repetitive thalamic stimulation in animals (143).

The thalamic syndrome in the human has been reproduced in the monkey by a small alumina cream lesion in the centromedian with subsequent alleviation by postcentral cortical excision (145). A somewhat similar problem in the human has been successfully treated by a localized electrolytic lesion in the thalamus (135). During the course of the latter procedure, it is of interest that thalamic stimulation in the conscious human subject did not produce any marked sensory phenomena, but did evoke typical, rhythmic movements very similar to those seen in choreoathetosis.

*Hypothalamus.*—The anatomy of these nuclei in various forms is becoming clearer (146, 147), and studies of hypothalamic function continue to provide information regarding a large and powerful feedback circuit involved in the preservation of the internal environment. The regulation of water balance starts at "osmoreceptors" which are located somewhere in the vascular bed of the internal carotid artery (148). The relay stations are apparently in the hypothalamus, as electrical stimulation of the supraoptico-hypophyseal tract in the conscious rabbit will cause the appearance of an antidiuretic substance in the urine (149, 150).

Stimulation of the tuber cinereum will also induce ovulation, whereas similar stimulation of the anterior pituitary or of the infundibular stem for prolonged periods has no such effect (151). The hypothalamic control of body temperature and arterial pressure is described (152) and the role of the hypophysis to carbohydrate and basal metabolism (153). The failure of lesions of the ventromedial nuclei, resulting in manic cats, to alter the electroencephalogram (154) confirms the relative independence of cortex and hypothalamus (155).

#### BRAIN STEM

*Tremor.*—Rhythmicity of function of many portions of the nervous system seems to be allied to activity in the structurally undifferentiated core of the brain stem which is known as the

reticular formation. Injury to the tegmentum of the upper brain stem produces, in monkeys, a tremor at rest, which appears identical with that of Parkinson's disease in man (156). The tremor returns with motor power after lesions of cortical areas 4 and 6 and is unaffected by interrupting recurrent pallidal connections to the cortex. It is postulated that the lesion blocks those impulses that, converging on more caudal parts of the reticular system, normally keep it in a steady state. The postulate that the alternating activity occurs in reticulospinal systems rather than previously described reverberating paths is substantiated in part by the observation that striatal activity is relatively independent of electroencephalographic phenomena and shows no relation to tremor in the human (157, 158). From a study of tremor in the human, Bishop *et al.* (159) conclude that the modification of the total pattern of pyramidal discharge to the cord level so alters the state of the internuncial system that clonic activity results. This may be viewed as a manifestation of such normal cord functional components as stretch reflex action, reciprocal innervation, etc., which are normally useful in other actions than tremor, but which result in tremor when the balance of normal forces acting at the cord level is altered. These concepts do not encourage surgical attacks on tremor at supratentorial levels (160, 161, 162).

This phenomenon of spontaneous rhythmic activity is of special interest because certain interesting comparisons can be drawn to the field of servomechanisms. In the latter, when one or more feedback loops exist, it is possible to adjust the nature and amount of feedback to give great stability, but the system then becomes sluggish and relatively inaccurate in its response. Conversely, when the nature and amount of feedback are adjusted to give great accuracy and rapidity of response, the system rapidly approaches a condition of instability of one kind or another. It seems that nature has also been forced to consider this dilemma, as the process of survival in primates has placed a premium on accuracy and rapidity of phasic movement. In order to accomplish this, our nervous systems have had to pay the penalty of potential instability. Thus, relatively minute lesions can result in a break in stability with spontaneous oscillation or tremor. In electronic systems, one way of influencing such oscillating activity is to decrease the amplifier in the feedback loop. It is quite possible that we accomplish just that by the use of drugs belonging to the bella-

donna group. In any case, this phenomenon should serve as a valuable tool in investigating such properties of the brain as oscillation, stability, etc.

*Reticular formation.*—Though little more is known regarding the connections of the reticular formation (163, 164), the functional organization of this system is being clarified. Lesions of any part of the suppressor system (i.e., suppressor areas of cortex, caudate, anterior lobe of cerebellum or fastigial nuclei, medial reticular formation) will result in spasticity (165, 166). This spasticity is maintained by facilitatory influx to the cord, conducted by reticulospinal and vestibulospinal tracts coursing chiefly in the ventral half of the lateral and in the ventral funiculi (167). The same mechanism was previously postulated to account for decerebrate rigidity. As confirmation of the latter, the facilitatory and suppressor reticulospinal connections have been shown to exert the same respective influences on stretch reflexes that were earlier observed on other types of motor activity (168). Sprague *et al.* (168) report that these influences are exerted upon flexor and extensor activity alike and hence are nonreciprocal, while Bach (169) states that stimulation of the bulbar suppressor system causes a diminution in the degree of both reflex contraction of agonist and reflex inhibition of antagonist. Since the effect on reflex responses and on decerebrate rigidity differ, one must postulate that two different processes of inhibition may be obtained at the motoneuron. Although it is definite that the vestibular complex contributes an ipsilateral facilitatory influence (168), this effect is minimal in the chronic preparation (170). It is possible that these findings are also related to the "generalized inhibition of Richet" (171, 172).

Activation of the multineuronal reticular circuits also has an effect on the general electrical activity of the cortex (173, 174), but the relationship of this to the general problem of feedback circuits remains to be elucidated.

The relation of periaqueductal lesion to coma (175, 176), the pathways subserving heat maintenance (177), and studies of the central tegmental tract (178) and fields of Forel (179) have also appeared. Discrete localization exists in certain cranial nerve nuclei (180 to 183).

#### CEREBELLUM

The sensory projections to the cerebellum are now well estab-

lished, and investigation has turned to the study of the interrelationship between them and the sensory areas of the cortex (184, 185). This connection is close and is apparently a two-way circuit. It is possible that the somatic cortical area I and the somatic II cerebellar projection area are interconnected, and, similarly, somatic II and the somatic I cerebellar projection area (186). The interconnections between cortical and cerebellar auditory and visual areas are also close (184, 185). The rather diffuse projection from the parietal association areas to the entire cerebellum is a further indication of the interdependence of the cerebral and cerebellar cortices.

The projection of the pupillary fields in area 24 to the contralateral cerebellar hemisphere (186) may explain the rather marked pupillary dilatation seen after lesions of the roof nuclei of the cerebellum (187). The loss of placing responses after similar lesions (187) and impairment of weight discrimination following lesions of the cerebellar hemispheres (188) indicate that the sensory projection to the cerebellum is of practical importance.

Analysis of the action potentials of the cerebellar cortex is under way (189 to 192), and the differential response to stimulation at varying frequencies has also been reaffirmed (193).

#### SPINAL CORD

The occasional clinical report of dissociation between pain and temperature sensation with discrete cord lesions (194) indicates that certain details of spinothalamic tract organization are not yet known. Similarly, the fact that section of the dorsal columns will relieve painful phantom limb with no disturbance of touch (195) is somewhat surprising, especially when coupled with the observation that posterior column section in the dog causes a rise in pain threshold (196). It is also possible that certain of the suppressor pathways run in the same region (197).

Whether or not the cord is capable of functional adaptation or "learning" has still not been entirely settled (198), especially in view of the fact that the unilateral spastic posture secondary to a cortical lesion is not abolished by subsequent transection of the cord provided one waits for a period of seven hours (199). Apparently, cerebral decortication is followed by "functional changes" in the spinal centers, and these changes persist even when impulses from supraspinal formations are abolished. The possible cyto-

chemical correlates of such changes have also been described (200).

Renshaw & Rosenbaum (201) have reinvestigated the Porter phenomenon and have shown that the bulbospinal fibers of respiratory function descend on the intact side of the cord and make connections with phrenic motoneurons of the opposite side. These crossed connections are less powerful than the uncrossed, and thus intensity of respiratory discharge will determine whether or not both phrenic nerves will be active under such conditions. This intensity is related to ventilation, and the Porter phenomenon can be explained on that basis. Since it is also known that many motoneurons send dendrites through the anterior commissure into the opposite half of the cord (202), it is perhaps surprising that more bilaterality of innervation does not exist.

The details of synaptic inhibition (203, 204, 205) will be dealt with in another chapter, including the evidence that triggering may occur exclusively at the axon hillock (206). Studies have also been published regarding the electrical activity of the spinal cord in shock (207) and the segmental distribution of cutaneous nerves in man (208).

#### PERIPHERAL NERVE

Sinclair, Weddell & Feindel (209) have postulated that an essential factor in the production of referred pain is the existence of branching among the pathways subserving pain. This branching is of such a type that one limb of a branched axon passes to the site of origin of the disturbance, and others pass to the sites to which the pain is referred. This mechanism works in two ways: first, by leading to a misinterpretation by the central nervous system of the true origin of the pain impulses; and, secondly, by the liberation of metabolites at the terminals in the region where pain is experienced, thus giving rise to secondary pain impulses actually having origin at the periphery.

An important advance in our understanding of the structure of nerve has been given by electron microscope studies. De Robertis & Schmitt (210, 211) have shown that the axis cylinders of individual nerve fibers are in actuality composed of many "neurotubules"—structures whose width lies in the vicinity of 500 to 700 Å, and having a wall of high density and a core of very low density. They possess cross-bands which form an axial repeating pattern, the period of which varies between 400 and 800 Å.

Nerve degeneration, as indicated both by loss of ability to conduct the impulse and by typical histological changes, is related temporally, if not causally, to disintegration of neurotubules. The impact of these findings, if they are substantiated, on the theory of conduction of the nerve impulse remains to be seen.

## LITERATURE CITED

1. SAWYER, W. W., *Mathematician's Delight*, 183 pp. (Penguin, London, 1943)
2. ROSENBLUETH, A., AND WIENER, N., *Philosophy Sci.*, **12**, 316-19 (1945)
3. WIENER, N., *Cybernetics*, 194 pp. (John Wiley & Sons, New York, 1948)
4. FRANK, L. K., HUTCHINSON, G. E., LIVINGSTON, W. K., McCULLOCH, W. S., AND WIENER, N., *Ann. N. Y. Acad. Sci.*, **50**, 187-278 (1948)
5. WILLIAMS, R. W., *Science Progress*, **37**, 42-52 (1949)
6. JEFFERSON, G., *Brit. Med. J.*, **II**, 1105-10 (1949)
7. HOAGLAND, H., *Science*, **109**, 157-64 (1949)
8. ASHBY, W. R., *E.E.G. Clin. Neurophysiol.*, **1**, 116-17 (1949)
9. PITTS, W., AND McCULLOCH, W. S., *Biometrics Bull.*, **4**, 91-99 (1948)
10. McCULLOCH, W. S., AND PITTS, W., *J. Am. Statistical Assoc.*, **4**, 91-99 (1948)
11. McCULLOCH, W. S., *Ann. N. Y. Acad. Sci.*, **50**, 259-77 (1948)
12. SHIMBEL, A., AND RAPOPORT, A., *Bull. Math. Biophys.*, **10**, 41-55 (1948)
13. SHIMBEL, A., *Bull. Math. Biophys.*, **10**, 131-43 (1948)
14. ROBERTS, T. B., *Bull. Math. Biophys.*, **10**, 1-10 (1948)
15. CULBERTSON, J. T., *Bull. Math. Biophys.*, **10**, 31-40 (1948)
16. ROSENBLUETH, A., WIENER, N., PITTS, W., GARCÍA RAMOS, J., AND WEBSTER, F., *J. Cellular Comp. Physiol.*, **32**, 275-318 (1948)
17. GOLD, T., AND PUMPREY, R. J., *Proc. Roy. Soc. (London)* [B]**135**, 462-91 (1948)
18. GOLD, T., *Proc. Roy. Soc. (London)* [B]**135**, 492-98 (1948)
19. WALTER, V. J., AND WALTER, W. G., *E.E.G. Clin. Neurophysiol.*, **1**, 57-86 (1949)
20. KLEITMAN, N., *Physiol. Revs.*, **29**, 1-30 (1949)
21. GOODWIN, C. W., AND STEIN, S. N., *Science*, **108**, 507 (1948)
22. GOLDMAN, S., VIVIAN, W. E., CHIEN, C. K., AND BOWERS, H. N., *Science*, **108**, 720-23 (1948)
23. BUCY, P. C., *The Precentral Motor Cortex*, 615 pp. (Univ. of Illinois Press, Urbana, 1949)
24. FEINDEL, W. H., ALLISON, A. C., AND WEDDELL, G., *J. Neurol. Neurosurg. Psychiat.*, **11**, 227-42 (1948)
25. FRENCH, J. D., SUGAR, O., AND CHUSID, J. G., *J. Neurophysiol.*, **11**, 185-92 (1948)
26. CHUSID, J. G., SUGAR, O., AND FRENCH, J. D., *J. Neuropath. Exptl. Neurol.*, **7**, 439-46 (1948)
27. SUGAR, O., FRENCH, J. D., AND CHUSID, J. G., *J. Neurophysiol.*, **11**, 175-84 (1948)
28. FOX, C. A., FISHER, R. R., AND DESALVA, S. J., *J. Comp. Neurol.*, **89**, 245-78 (1948)
29. FISHER, R. R., AND DESALVA, S. J., *Anat. Record*, **100**, 660 (1948)

30. LOCKARD, I., *J. Comp. Neurol.*, **89**, 349-86 (1948)
31. GAY, J. R., AND GELLHORN, E., *Proc. Soc. Exp. Biol. Med.*, **70**, 711-18 (1949)
32. PENFIELD, W., AND RASMUSSEN, T., *Arch. Neurol. Psychiat.*, **61**, 21-27 (1949)
33. ROTH, M., *Brain*, **72**, 89-111 (1949)
34. ADES, H. W., AND RAAB, D. H., *J. Neurophysiol.*, **12**, 101-8 (1949)
35. SPERRY, R. W., *Physiol. Zool.*, **21**, 351-61 (1948)
36. SPERRY, R. W., *Anat. Record*, **102**, 63-75 (1948)
37. BARRON, D. H., *Anat. Record*, **100**, 639 (1948)
38. DENNY-BROWN, D., AND BOTTERELL, E. H., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 235-345 (1948)
39. METTLER, F. A., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 162-99 (1948)
40. WOOLSEY, C. N., SETTLAGE, P. H., SUCKLE, H. M., AND BINGHAM, W. G., *Federation Proc.*, **8**, 172 (1949)
41. CHUSID, J. G., DEGUTIERREZ-MAHONEY, C. G., AND ROBINSON, F., *Federation Proc.*, **8**, 25 (1949)
42. SETTLAGE, P. H., BINGHAM, W. G., SUCKLE, H. M., BERGE, A. F., AND WOOLSEY, C. N., *Federation Proc.*, **8**, 144 (1949)
43. RASMUSSEN, T., AND PENFIELD, W., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 346-61 (1948)
44. GELLHORN, E., *Brain*, **72**, 35-62 (1949)
45. GELLHORN, E., *Brain*, **71**, 26-33 (1948)
46. CLARK, G. W., AND WARD, J. W., *Brain*, **71**, 332-42 (1948)
47. LASSEK, A. M., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 106-28 (1948)
48. VERHAART, W. J. C., *J. Comp. Neurol.*, **88**, 139-55 (1948)
49. WOOLSEY, C. N., AND CHANG, H.-T., *Research Pubs., Assoc. Research Nervous Nervous Mental Diseases*, **27**, 146-61 (1948)
50. BROOKHART, J. M., AND MORRIS, R. E., *J. Neurophysiol.*, **11**, 387-98 (1948)
51. GLEES, P., AND COLE, J., *J. Physiol.*, **108**, 33 (1949)
52. JANZEN, R., *Deut. Z. Nervenheilk.*, **158**, 525-42 (1948)
53. SARKISOV, S. A., *Nevropatol. i. Psikiat.*, **17**, 7-17 (1948)
54. CLARK, G., *Brain*, **71**, 320-31 (1948)
55. PENFIELD, W., *E.E.G. Clin. Neurophysiol.*, **1**, 3-10 (1949)
56. SCOVILLE, W. B., *J. Neurosurg.*, **6**, 65-73 (1949)
57. METTLER, F. A., *Federation Proc.*, **8**, 109 (1949)
58. PENFIELD, W., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 519-33 (1948)
59. LEWIS, N. D. C., *Am. J. Psychiat.*, **105**, 151 (1948)
60. LEBEAU, J. L. E., FELD, M., AND BOUVET, M., *Rev. neurol.*, **80**, 481-96 (1948)
61. HEATH, R. G., AND POOL, J. L., *Psychosomat. Med.*, **10**, 254-56 (1948)
62. POOL, J. L., HEATH, R. G., AND WEBER, J. J., *Bull. N. Y. Acad. Med.*, **25**, 335-44 (1949)
63. JONES, C. H., AND SHANKLIN, G. J., *Northwest Med.*, **47**, 421-27 (1948)
64. STROM-OLSEN, R., AND TOW, P. M., *Lancet*, **256**, 87-90 (1949)
65. WARD, A. A., JR., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 438-45 (1948)

66. RUSSELL, W. R., *Lancet*, **254**, 356-60 (1948)
67. STANLEY, W. C., AND JAYNES, J., *Psychol. Rev.*, **56**, 18-32 (1949)
68. HALSTEAD, W., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 59-66 (1948)
69. SETTLAGE, P. H., ZABLE, M., AND HARLOW, H. F., *J. Exptl. Psychol.*, **38**, 50-65 (1948)
70. HARLOW, H. F., AND SETTLAGE, P. H., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 446-59 (1948)
71. CRAWFORD, M. P., FULTON, J. F., JACOBSEN, C. F., AND WOLFE, J. B., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 3-58 (1948)
72. VONBONIN, G., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 67-83 (1948)
73. BAILEY, P., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 84-94 (1948)
74. BECK, E., *J. Anat.*, **83**, 147-57 (1949)
75. MCCULLOCH, W. S., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 95-105 (1948)
76. VONBONIN, G., AND GREEN, J. R., *J. Comp. Neurol.*, **90**, 243-54 (1949)
77. CLARK, W. E. LE G., *Lancet*, **255**, 353-56 (1948)
78. ROSE, J. E., AND WOOLSEY, C. N., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 210-32 (1948)
79. FREEMAN, W., AND WATTS, J. W., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 200-9 (1948)
80. HASSLER, R., *Nervenarzt*, **19**, 9-12 (1948)
81. LIVINGSTON, R. B., FULTON, J. F., DELGADO, J. M. R., SACHS, E., JR., BRENDLER, S. J., AND DAVIS, G. D., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 405-20 (1948)
82. LIVINGSTON, R. B., CHAPMAN, W. P., LIVINGSTON, K. E., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 421-32 (1948)
83. CHAPMAN, W. P., LIVINGSTON, R. B., AND LIVINGSTON, K. E., *J. Clin. Invest.*, **27**, 529 (1948)
84. DELGADO, J. M. R., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 433-37 (1948)
85. KAADA, B. R., PRIBRAM, K. H., AND EPSTEIN, J. A., *Federation Proc.*, **8**, 83-84 (1949)
86. HOFF, E. C., *Confinia Neurol.*, **9**, 166-76 (1949)
87. SHENKIN, H. A., WOODFORD, R. B., FREYHAN, F. A., AND KETY, S. S., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 823-31 (1948)
88. REED, J., *Gastroenterology*, **10**, 118-19 (1948)
89. SWEET, W. H., COTZIAS, G. C., SEED, J., AND YAKOVLEV, P., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 795-822 (1948)
90. REITMAN, F., *Brit. Med. J.*, **II**, 1064 (1948)
91. GARDNER, W. D., AND FOX, C. A., *Anat. Record*, **100**, 663-64 (1948)
92. SMITH, W. K., *Anat. Record*, **100**, 713 (1948)
93. ROSE, J. E., AND WOOLSEY, C. N., *J. Comp. Neurol.*, **89**, 279-348 (1948)
94. MARBURG, O., *Confinia Neurol.*, **9**, 211-16 (1949)
95. ALLEN, W. F., *J. Comp. Neurol.*, **88**, 425-38 (1948)
96. POOTZL, O., *Monatsschr. Psychiat. Neurol.*, **117**, 153-70 (1949)

97. BARD, P., AND MOUNTCASTLE, V. B., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 362-404 (1947)
98. GIBBS, E. L., GIBBS, F. A., AND FUSTER, B., *Arch. Neurol. Psychiat.*, **60**, 331-39 (1948)
99. BENFIELD, W., *Arch. Neurol. Psychiat.*, **60**, 107-18 (1948)
100. BECKETT, S., AND GELLHORN, E., *Am. J. Physiol.*, **153**, 113-20 (1948)
101. HECAEN, H., DAVID, M., AND TALAWACH, J., *Rev. neurol.*, **79**, 726 (1948)
102. MARSHALL, W. H., *Federation Proc.*, **8**, 107 (1949)
103. WHIELDON, J. A., AND VAN HARREVELD, A., *Federation Proc.*, **8**, 164 (1949)
104. WARD, A. A., JR., MCCULLOCH, W. S., AND KOPELOFF, N., *J. Neurophysiol.*, **11**, 377-86 (1948)
105. MCCULLOCH, W. S., *E.E.G. Clin. Neurophysiol.*, **1**, 19-27 (1949)
106. JASPER, H. H., *E.E.G. Clin. Neurophysiol.*, **1**, 11-18 (1949)
107. DROOGLEEVER, F. J., *Nederland Tijdschr. Geneesk.*, **92**, 1189-96 (1948)
108. GELLHORN, E., *Federation Proc.*, **8**, 55 (1949)
109. KLEIN, R., AND EARLY, D. F., *J. Mental Sci.*, **94**, 581-89 (1948)
110. GELLHORN, E., AND BALLIN, H. M., *Arch. Neurol. Psychiat.*, **59**, 718-33 (1948)
111. PARSONS-SMITH, G., *J. Neurol. Neurosurg. Psychiat.*, **11**, 267-70 (1948)
112. HYDE, J., BECKETT, S., AND GELLHORN, E., *J. Neurophysiol.*, **12**, 17-27 (1949)
113. DARROW, C. W., *E.E.G. Clin. Neurophysiol.*, **1**, 25-27 (1949)
114. GYARFAS, K., POLLOCK, G. H., AND STEIN, S. N., *Proc. Soc. Exptl. Biol. Med.*, **70**, 292-93 (1949)
115. STEIN, S. N., AND POLLOCK, G. H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 290-91 (1949)
116. POLLOCK, G. H., STEIN, S. N., AND GYARFAS, K., *Proc. Soc. Exptl. Biol. Med.*, **70**, 291-92 (1949)
117. ELLIOTT, K. A. C., *E.E.G. Clin. Neurophysiol.*, **1**, 29-31 (1949)
118. WALKER, A. E., AND JOHNSON, H. C., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 460-77 (1948)
119. TOMAN, J. E. P., *E.E.G. Clin. Neurophysiol.*, **1**, 33-44 (1949)
120. TORDA, C., AND WOLFF, H. G., *J. Pharmacol. exptl. therap.*, **95**, 444-47 (1949)
121. BREMER, F., *E.E.G. Clin. Neurophysiol.*, **1**, 177-93 (1949)
122. BRAZIER, M. A. B., *E.E.G. Clin. Neurophysiol.*, **1**, 195-204 (1949)
123. TEN CATE, J., HORSTEN, G. P. M., AND KOOPMAN, L. J., *E.E.G. Clin. Neurophysiol.*, **1**, 231-35 (1949)
124. MERLIS, J. K., AND WATSON, C. W., *Arch. Neurol. Psychiat.*, **61**, 695-98 (1949)
125. GIBBS, F. A., AND KNOTT, J. R., *E.E.G. Clin. Neurophysiol.*, **1**, 223-29 (1949)
126. LENNOX, W. G., *E.E.G. Clin. Neurophysiol.*, **1**, 45-51 (1949)
127. SWANK, R. L., *J. Neurophysiol.*, **12**, 161-72 (1949)
128. GARVIN, J. S., AND AMADOR, L. V., *Federation Proc.*, **8**, 53-54 (1949)
129. CHANG, H.-T., AND FULTON, J. F., *E.E.G. Clin. Neurophysiol.*, **1**, 249-50 (1949)
130. GASTAUT, H., *E.E.G. Clin. Neurophysiol.*, **1**, 205-21 (1949)
131. GELLHORN, E., AND BALLIM, H. M., *Arch. Neurol. Psychiat.*, **59**, 496-503 (1948)

132. FORBES, A., BATTISTA, A. F., CHATFIELD, P. O., AND GARCIA, J. P., *E.E.G. Clin. Neurophysiol.*, **1**, 141-75 (1949)
133. WOODBURY, L. A., *Federation Proc.*, **8**, 172 (1949)
134. SPIEGEL, E. A., WYCIS, H. T., FREED, H., AND LEE, A. J., *Proc. Soc. Exptl. Biol. Med.*, **69**, 175 (1948)
135. TALAIRACH, J., HECAEN, H., DAVID, M., MONNIER, M., AND DEAJURIAGUERRA, J., *Rev. neurol.*, **81**, 4-24 (1949)
136. COMBS, C. M., *Anat. Record*, **100**, 651 (1948)
137. McLARDY, T., *Brain*, **71**, 290-303 (1948)
138. GLEES, P., AND WALL, G. D., *J. Comp. Neurol.*, **88**, 129-37 (1948)
139. MOUNTCASTLE, V., AND HENNEMAN, E., *J. Neurophysiol.*, **12**, 85-100 (1949)
140. MOUNTCASTLE, V., AND HENNEMAN, E., *Federation Proc.*, **8**, 115 (1949)
141. KNIGHTON, R. S., *J. Comp. Neurol.* (In press)
142. WYCIS, H. T., LEE, A. J., AND SPIEGEL, E. A., *Confinia neurol.*, **9**, 264-72 (1949)
143. FIELDS, W. S., KING, R. B., AND O'LEARY, J. L., *J. Neurophysiol.*, **12**, 117-30 (1949)
144. CORT, J. H. (Personal communication)
145. WHITTIER, J. R., GRAHAM, S. E., AND KOPELOFF, N., *J. Neuropath. Exptl. Neurol.*, **8**, 93-99 (1949)
146. KRIEG, W. J. S., *J. Comp. Neurol.*, **88**, 1-51 (1948)
147. FEREMUTSCH, K., *Monatsschr. Psychiat. Neurol.*, **115**, 194-222 (1948)
148. VERNEY, E. B., *Brit. Med. J.*, **II**, 119-23 (1948)
149. HARRIS, G. W., *J. Physiol. (London)*, **107**, 412-17 (1948)
150. HARRIS, G. W., *J. Physiol. (London)*, **107**, 430-35 (1948)
151. HARRIS, G. W., *J. Physiol. (London)*, **107**, 418-29 (1948)
152. ROBBARD, S., *Science*, **108**, 413-15 (1948)
153. VERMUND, H., *Acta Med. Scand.*, **131**, 515-46 (1948)
154. WHEATLEY, M. D., KNOTT, J. R., AND INGRAM, W. R., *Proc. Soc. Exptl. Biol. Med.*, **70**, 16-19 (1949)
155. GELLHORN, E., *Proc. Soc. Exptl. Biol. Med.*, **70**, 107-8 (1949)
156. WARD, A. A., JR., McCULLOCH, W. S., AND MAGOUN, H. W., *J. Neurophysiol.*, **11**, 317-30 (1948)
157. MEYERS, R., HAYNE, R., AND KNOTT, J., *J. Neurol. Neurosurg., Psychiat.*, **12**, 111-23 (1949)
158. HAYNE, R., MEYERS, R., AND KNOTT, J. R., *J. Neurophysiol.*, **12**, 185-95 (1949)
159. BISHOP, G. H., CLARE, M. H., AND PRICE, J., *Applied Physiol.*, **1**, 123-47 (1948)
160. BROWDER, J., *Surg. Clin. N. Am.*, **4**, 390-95 (1948)
161. ALAJOUANINE, J., LE BEAU, J., AND HOUDART, R., *Rev. neurol.*, **79**, 137-38 (1947)
162. ALAJOUANINE, J., LE BEAU, J., AND HOUDART, R., *Rev. neurol.*, **79**, 134-37 (1947)
163. NIEMER, W. T., *Anat. Record*, **100**, 699-700 (1948)
164. BARNHART, M., RHINES, R., MCCARTER, J. C., AND MAGOUN, H. W., *Arch. Neurol. Psychiat.*, **59**, 368-77 (1948)

165. LINDSLEY, D. B., SCHREINER, L. H., AND MAGOUN, H. W., *J. Neurophysiol.*, **12**, 197-205 (1949)
166. KING, R. B., *J. Comp. Neurol.*, **89**, 207-23 (1948)
167. SCHREINER, L. H., LINDSLEY, D. B., MAGOUN, H. W., *J. Neurophysiol.*, **12**, 207-16 (1949)
168. SPRAGUE, J. M., SCHREINER, L. H., LINDSLEY, D. B., AND MAGOUN, H. W., *J. Neurophysiol.*, **11**, 501-7 (1948)
169. BACH, L. M. N., *Federation Proc.*, **8**, 6 (1949)
170. KEMBERLING, S. R., AND SPIEGEL, E. A., *Federation Proc.*, **8**, 84-85 (1949)
171. GEREBTZOFF, M. A., *Arch. intern. physiol.*, **55**, 293-94 (1948)
172. GEREBTZOFF, M. A., *Arch. intern. physiol.*, **56**, 286-310 (1949)
173. MORUZZI, G., AND MAGOUN, H. W., *Federation Proc.*, **8**, 113 (1949)
174. WARD, A. A., JR., *E.E.G. Clin. Neurophysiol.*, **1**, 120 (1949)
175. HESS, W. R., *J. physiol.*, **41**, 61-67A (1949)
176. MAGOUN, H. W., *Anat. Record*, **100**, 752 (1948)
177. KELLER, A. D., *Am. J. Physiol.*, **154**, 82-86 (1948)
178. VERHAART, W. J. C., *J. Comp. Neurol.*, **90**, 173-92 (1949)
179. FREY, E., AND BUCHER, V., *Schweiz. Arch. Neurol. Psychiat.*, **60**, 80-131 (1947)
180. SZENTAGOTHAJ, J., *J. Comp. Neurol.*, **90**, 111-20 (1949)
181. GETZ, B., AND SIRNES, T., *J. Comp. Neurol.*, **90**, 95-110 (1949)
182. PEARSON, A. A., *J. Comp. Neurol.*, **90**, 1-45 (1949)
183. BORISON, H. L., AND WANG, S. C., *Federation Proc.*, **8**, 13 (1949)
184. SNIDER, R. S., AND ELDRED, E., *Anat. Record*, **100**, 714 (1948)
185. SNIDER, R. S., COOKE, P. M., AND HENNEMAN, E., *Anat. Record*, **100**, 757 (1948)
186. HAMPSON, J. L., *J. Neurophysiol.*, **12**, 37-50 (1949)
187. CHAMBERS, W. H., *Anat. Record*, **100**, 649 (1948)
188. HALPERN, L., *Confinia neurol.*, **8**, 212-16 (1947-48)
189. MORUZZI, G., BROOKHART, J. M., AND SNIDER, R. S., *Federation Proc.*, **8**, 113 (1949)
190. SCHOEPFLE, G. M., *Federation Proc.*, **8**, 140 (1949)
191. JACOBS, J., AND SNIDER, R. S., *Federation Proc.*, **8**, 80 (1949)
192. DOW, R. S., *E.E.G. Clin. Neurophysiol.*, **1**, 249 (1949)
193. MORUZZI, G., *Boll. soc. ital. biol. sper.*, **24**, 753-55 (1948)
194. SHERMAN, I. C., AND ARIEFF, A. J., *J. Nervous Mental Disease*, **108**, 285-92 (1948)
195. BROWDER, J., AND GALLAGHER, J. P., *Ann. Surg.*, **128**, 456-69 (1948)
196. MORIN, G., DONNET, V., AND MAFFRE, S., *Compt. rend. soc. biol.*, **142**, 367-68 (1948)
197. MORIN, G., DONNET, V., AND MAFFRE, S., *Compt. rend. soc. biol.*, **142**, 691-92 (1948)
198. DEESE, J., AND KELLOGG, W. N., *J. Comp. Physiol. Psychol.*, **42**, 157-60 (1949)
199. ALELLA, A., *Arch. fisiol.*, **47**, 105-12 (1948)
200. HOCHBERG, I., AND HYDEN, H., *Acta. Physiol. Scand.*, **17**, 1-63 (1949)
201. RENSHAW, B., AND ROSENBAUM, H., *Anat. Record*, **101**, 738-39 (1948)

202. ASTROM, K. E., *Acta Physiol. Scand.*, **16**, 1-67 (1948)
203. BROOKS, C. McC., AND ECCLES, J. C., *J. Neurophysiol.*, **11**, 431-44 (1948)
204. BROOKS, C. McC., AND ECCLES, J. C., *J. Neurophysiol.*, **11**, 401-416 (1948)
205. BROOKS, C. McC., ECCLES, J. C., AND MALCOLM, J. L., *J. Neurophysiol.*, **11**, 417-430 (1948)
206. HUNTER, J., LILLIE, R., AND GESELL, R., *Federation Proc.*, **8**, 79 (1949)
207. HORSTEN, G. P. M., *Nederland Tijdschr. Geneesk.*, **3**, 3042 (1948)
208. KEEGAN, J. J., AND GARRETT, F. D., *Anat. Record*, **102**, 409-37 (1948)
209. SINCLAIR, D. C., WEDDELL, G., AND FEINDEL, W. H., *Brain*, **71**, 184 (1948)
210. DE ROBERTIS, E., AND SCHMITT, F. O., *J. Cellular Comp. Physiol.*, **31**, 1-23 (1948)
211. DE ROBERTIS, E., AND SCHMITT, F. O., *J. Cellular Comp. Physiol.*, **32**, 45-56 (1948)

# VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM<sup>1</sup>

BY ROBERT B. LIVINGSTON

*Laboratory of Physiology, Yale University School of Medicine,  
New Haven, Connecticut*

*at present*

*William B. Gruber Fellow in Neurophysiology, Institut  
Marey, Collège de France, Paris, France*

One of the most important contributions to knowledge of function of the nervous system during the past few years is to be found in the empirical generalizations of McCulloch and his colleagues who have reemphasized the potentialities of mutually interacting complexes. This discipline, newly named cybernetics gives impetus and authority to the growing accumulation of facts which emphasize the dynamic character of nerve net activity. It is not possible to embrace intellectually the total behavior of such a complicated organ as the brain, but cybernetics provides a higher level of still limited understanding. Hoagland (1) has recently summarized this contribution.

The total unity of the visceral nervous system has been portrayed by Yakovlev (2). Emphasis is given to the broad organizational relationships among the cortical, diencephalic, brain stem, medullary, and spinal visceral centers, and the peripheral visceral outflow, and between this whole ensemble and the remainder of the nervous system with which it is enmeshed functionally and anatomically.

A large number of analytical studies have been carried out on man following transection of the spinal cord, regional ablation of the cerebral cortex, cutting of tracts in various parts of the nervous system, localized destruction of thalamic nuclei, etc. A further cadre of evidence is derived from experiments which involve stimulation of and recording from the surface or even deeply buried structures in the nervous system of man. It can be seen that the distinction between animal and human experimentation is becoming attenuated. Furthermore, one can now begin to analyze visceral function by the same isolation of "levels" of activity, i.e., activity

<sup>1</sup> This review covers the period from July 1, 1948 until June 30, 1949. Unfortunately, many important articles and journals were not available to the author, and the appended list of references is therefore incomplete.

of spinal, decerebrate and decorticate preparations, which has been found so useful in analysis of the somatic motor system.

#### CEREBRAL CORTEX

There are certain cortical areas which appear to subserve visceral and skeletal activity simultaneously. These include the premotor cortex, frontal eye fields, some areas of the parietal and occipital cortex, etc. There are other cortical regions which appear to subserve visceral activity rather exclusively. These include the hippocampus, amygdala, tip of the temporal lobe, orbitomesial surface of the frontal lobe, and the subcallosal and cingulate gyri, which form a continuous ring of cortex on the medial and inferior surfaces of each hemisphere. It is suggestive that the first group of cortical areas coordinate visceral with somatic activities, and that the second group, collectively referred to as mesopallium by Yakovlev, play a rôle in the highest integrative patterns involved in visceral activity.<sup>2</sup>

*Ablation.*—Bard & Mountcastle (3) find that cats deprived of all cortex, except that roughly designated by the term mesopallium, are extraordinarily docile. When the hippocampal and amygdaloid portions of this remaining cortex are removed, lower centers are "released" and the extremely docile cats now show complex patterns of undirected rage even in response to nonnoxious stimuli. If the hippocampus and amygdala alone are removed from an otherwise intact animal, the rage behavior which ensues has benefit of intelligent direction.

Ablation of the anterior cingulate region results in extensive behavioral changes in primates. The behavior was described as reduction in reactions of fear and anger by Smith (4) and as lack of consciousness of social repercussions of actions by Ward (5).

<sup>2</sup> When considered in their subjective as well as objective aspects, the most highly integrated patterns of visceral activity constitute emotional behavior. Patients in whom these cortical regions or their pathways to and from lower visceral centers are interfered with, losing as they do some of the mechanisms involved in the integration of visceral drives with controlled and refined visceral activity, naturally show striking alterations of emotional behavior. It is to be expected that they show reduction in ability to maintain long-sustained emotional drive, that they exhibit loss of deep emotional feeling and refined emotional reaction, and that they lack "foresightedness". Both the good and bad aspects of frontal lobotomy are bound up in this fact.

Analogous behavioral change appears to follow undercutting this cortical area in man (5).

Removal of the posterior portion of the orbital gyrus in monkeys results in marked hyperactivity, quantitatively eight to sixteen times above control levels, and in increased temperature of the extremities (6). Of 40 human lobotomy cases, studied pathologically by Meyer, 22 had cuts sectioning bilaterally the posterior orbital surfaces, and 18 showed lesions involving the other prefrontal tracts, but sparing the orbital surfaces (7). In the former group there were six patients who exhibited generalized restlessness postoperatively: there were none in the second group. Seven of the 22 patients with posterior orbital sections showed marked vasomotor and trophic changes and some of them showed prolonged hyperpyrexia not otherwise accounted for; there were no such effects in the control group. Netsky & Starr (8) report vasomotor and sudomotor hyperactivity contralateral to the side of traumatic brain lesions near the lateral extent of the orbital surface in man. Reitman (9) reports significant reduction in 17-ketosteroid excretion following lobotomy. The occasional metabolic catastrophe, such as that described by Sweet *et al.* (10), which may follow frontal lobotomy, underlines the importance of the frontal lobe to widespread visceral functions.

*Stimulation.*—Electrical excitation in animals and man has revealed analogous autonomic responses from the cingulate gyrus (4, 5, 11, 12, 13), the orbital surface of the frontal lobe (6, 11, 12, 14, 15, 16) and the tip of the temporal lobe (11, 12). The responses involve both vascular and respiratory effects, although some experiments indicate that a much richer mine of representations such as pupillary response, sudomotor activity, etc., should be included. In addition, the cingulate gyrus in both animals and man has been shown to play a rôle in control of electrical activity of other parts of the brain and in certain aspects of general somatic muscular tension (4, 5, 13).

Allen (17) obtained respiratory and vascular changes on stimulation of the hippocampus in dogs. Delgado has pointed out that some regions of frontal cortex infolded within sulci have similar functional representation in the dog and monkey (18). The vascular and respiratory effects are separable functionally (6, 15) and follow different pathways in the hypothalamus (12).

Although the patterns of visceral response elicited by electrical

excitation are slightly different in the different regions, there is no question of the essential functional unity of this whole band of mesopallium (12).

Hoff, Kell *et al.* (19) repeated Hoff & Green's experiments of 1936 in which profound changes had been evoked in the oncometer size of the kidney by cerebral cortical excitation in the cat. In their recent communication, they confirm Cort's (20) observations that appropriate cortical stimulation can result in severe renal cortical ischemia involving the so-called Oxford shunt. The cortical areas from which such responses can be obtained appear to include the cat's sensorimotor cortex as well as parts of the mesopallium. The initiation by insulin hypoglycemia of gastric hypotonia and reduced motility appears to depend on medullary vagal centers and not on higher structures, according to Jögi, Ström & Uvnäs (21). Decortication had no effect on gastric secretory activity following insulin, according to Ström & Uvnäs, but electrical excitation of the frontal lobes of cats caused inhibition of gastrointestinal motility (22). Davy *et al.* (23) have localized cortical control of gastrointestinal motility and gastric acid secretion in the region of the frontal eye fields of the monkey.

#### THE DIENCEPHALON

The intimate fibrillary connections among the cells of the septum, preoptic zone, hypothalamus and subthalamus, so closely and intimately bind the whole region according to Mosinger (24) that it should be considered one functional unit which he refers to as the enlarged subthalamus. Hayne, Meyers & Knott (25), in studying recordings of electrical activity deep within the brain of man, come to the conclusion that the corpus striatum, putamen, head of the caudate nucleus, globus pallidum, subcallosal bundle and the anterior limb of the internal capsule all function in electrical concert as far as frequency, amplitude and wave form are concerned. Hess's extensive studies (26, 27) of the somatic and autonomic responses which can be elicited by electrical stimulation of diencephalon in the unanesthetized cat, support the contention that anatomic distinctions between hypothalamus and thalamus do not have any rigid and restrictive importance from a functional point of view. Since most of the fibers are short, and the synapses are very numerous, to establish a new record in understatement, it is likely that activity spreads rather slowly and diffusely.

McCulloch reviews work which identified the functional con-

nections between the frontal cortex and subthalamic and hypothalamic centers (28), and additional evidence is provided in the studies of Sachs & Brendler (14), and Fulton, Pribram *et al.* (12). Mettler, in a spirited essay on nonpyramidal projections (29), stresses the continuity of autonomic activity from cerebral cortex to spinal cord. Rose & Woolsey (30, 31), von Bonin & Green (32), Minkowski (33), McLardy (34), Freeman & Watts (35), among others, describe the anatomical connections between the frontal cortex and diencephalic structures in the rabbit, sheep, cat, monkey and man. LeGros Clark emphasizes how much we do not know about the relationship of the mammillary body and anterior thalamic nucleus, on the one hand, with the limbic lobe, hippocampus and fornix, on the other (36). The connections in this complex undoubtedly provide one of the most important and least understood links between mesopallium and diencephalon. Autonomic changes following thalamotomy in man are described by Spiegel *et al.* (37).

Buchanan & Hill (38) relate the time of functional maturation of thermoregulation in the hamster to the development of myelination of the hypothalamus. Lundback (39) discusses hypothalamic adiposity in the rat, and Brobeck (40) relates food intake to temperature regulatory function. A whole series of exciting papers on heat regulation as a hypothalamic function in relation to food intake, water metabolism, and other processes, has been published by Rodbard (41), Bonvallet *et al.* (42, 43), Stutinsky (44), Janowitz *et al.* (45), Archdeacon *et al.* (46), Harris (47, 48, 49), Hillarp (50), O'Connor (51), Folkow *et al.* (52), Abrams *et al.* (53) and others. Keller (54) traces descending fibers which are involved in heat maintenance, and Folkow, Ström & Uvnäs (55) state that the cutaneous vasodilatation following localized heating of the anterior hypothalamus involves, finally, the sympathetic outflow. Koella has succeeded in obtaining suppression of urine secretion by well localized, low intensity stimulation in the anterior hypothalamus of the cat (56). There is probably both a direct nervous and a hormonal effect initiated by such stimulation. Sawyer, Markee *et al.* (57, 58) have studied the nervous reflex mechanisms involved in induced ovulation of the rabbit and the cyclic neural drive of hormonal activity in the spontaneously ovulating rat.

Bonvallet, Dell & Stutinsky describe rage and fear reactions in dogs with localized hypothalamic lesions (59). Bender, Furlow & Teuber (60) record superficially analogous behavior in a war

veteran who has a large foreign body balloting in his third ventricle.

Schachter & Schachter (61) succeed in causing in dogs the rapid development of gastrointestinal ulceration, intussusception and bleeding, and ulcerations of the mouth consequent to pressure applied against the hypothalamus by means of glass beads inserted intradurally. The lesions are more likely to occur and are more drastic if the pressure is exerted on the hypothalamus or adjacent brain stem, although similar lesions may follow imbedding of the beads in the hippocampal region.

Autonomic reflex patterns are altered after electroshock therapy (62). Patients with electroencephalographic (EEG) evidence of hypothalamic or subthalamic disease often exhibit excessive sweating, vasomotor hyperactivity and gastrointestinal symptomatology in addition to transient interferences with the state of consciousness (63). An epileptic made worse by sedative drugs was found by Caveness to have an increasingly abnormal EEG as depth of normal sleep advanced (64). Kleitman, (65), Hess (66), and Kayser (67) summarize and discuss theories of sleep and Hess produces convincing "sleep" in cats by a brief period of hypothalamic stimulation. Excitation in a restricted zone elicits a co-ordinated and habitual pattern of "going to sleep" activity from which the animal may be roused by the odor of fresh meat placed in front of its nose, but not by noise or fairly vigorous handling. After arousal by meat, the cat will eat, lick its chops and curl up for slumber once more. Hess contrasts this co-ordinated, restorative induced sleep with induced adynamia, coma, narcosis and hypnosis.

#### BRAIN STEM AND MEDULLA

Henneman observes that the reticulum formation contains a region subserving bladder control (213). Borison & Wang (68) have localized in the dorsolateral portion of the lateral reticular formation a region which, when destroyed, eliminates or seriously impairs response to apomorphine. Essig, Hampson *et al.* (69) relate Bard's flocculonodular lobe motion sickness center of the cerebellum to mechanisms responsible for labyrinthine response to diisopropylfluorophosphate (DFP) injected into the carotid. Section of the eighth cranial nerve or extirpation of the labyrinth on the side of injection abolishes response from that side. They present further evidence to show that the vestibular mechanism is cholinergic in nature. In a study of human pathological material, Atkinson con-

cludes that ischemia of the lateral tegmental area of the pons will lead to a marked rise in arterial pressure, brain swelling and edema of the lungs (70). Gernandt has recorded from three different types of single nerve fibers in the vestibular nerve: (a) fibers which are excited by rotation toward the side of recording and made inactive by rotation in the opposite direction, (b) fibers which are excited by rotation in either direction, and (c) fibers which are made inactive on rotation in either direction (71). Bonvallet & Dell (72) suggest that there may be a denominator common to many different vertebrates in the precise threshold of respiratory center activity, at which thermally induced polypnea is instituted. Hall, Attardo & Perryman report on the influence of dinitrophenol on such a polypnea threshold (73). Getz & Sirius have shown that the dorsal motor nucleus of the vagus has definite topographical localization for its different areas of peripheral distribution (74).

#### SPINAL CORD

Spinal man shows over-reactivity of reflex behavior below the level of cord transection. Thompson & Witham (75) find that in spinal man, various stimuli, principally vesical and rectal in origin, and most marked in cases of high spinal lesion, may set off paroxysmal bouts of hypertension. Pollock, Boshes *et al.* (76) recently systematically examined some of these reflex responses. Whereas orthostatic hypotension is exaggerated, cold immersion of the foot leads to temporary reflex hypertension. Bladder distension evokes excessive sweating. The absence of central connections for temperature regulation results in a state of poikilothermia below the transection. Similar mass reflex responses are discussed by Schumacher *et al.* (77) in relation to headache, facial flushing, marked rise in arterial pressure, slowing of the pulse, sudomotor and pilomotor hyperactivity. Munro, Horne & Paull (78, 79) record that spinal man may remain sexually potent and fertile if the sympathetic outflow from T6 to L3 is preserved. Even if potency or ejaculation is precluded by nerve or cord mutilation, fertility may be retained.

Sweating in normal man takes place in small bursts of activity at about 6 to 7 per min. during moderate sweat activation, according to Albert & Palmes (80). Since different skin areas show synchronous sweating rhythms, it appears that there must be widespread rhythmic discharge of some central nervous mechanism.

Malméjac, Chardon & Gross (81) have demonstrated vasocon-

striction arising from spinal centers, initiated by hypoxia in dogs with the spinal cord sectioned at C4. They prove that this response is mediated by nervous outflow rather than by hormonal influences or direct effect of a lack of oxygen on the vessels by employing crossed circulation to the limbs studied.

#### PERIPHERAL NERVOUS STRUCTURES

*Preganglionic neurons and sympathetic ganglia.*—Emmelin & MacIntosh (82) report recovery of rather constant quantities of acetylcholine following stimulation of preganglionics, in spite of the use of different perfusates, and conclude that release of acetylcholine is a physiological mechanism involved in synaptic activity. This constitutes ancillary evidence but not proof. Lorente de N6 & Laporte (83) prove that presynaptic impulses can exert a direct and long lasting inhibitory as well as excitatory action upon ganglion cells of the turtle. Stellate ganglia of the squid, on the other hand, do not show integrative action until "fatigue" sets in, at which time facilitation can be demonstrated (84).

Wiersma & Schallek (85) compare the action of different drugs on synaptic transmission in the crayfish, and Posternak & Larabee (86) have compared the actions of different narcotics on synapses and axons in the cat sympathetic ganglia. They also describe the depressant action of natural epinephrine on synaptic transmission (87). On stimulation of frog preganglionics, Saunders & Sinclair (88) find that the postganglionic potentials are similarly altered by changing either potassium or hydrogen ion concentration in the perfusate. Marrazzi (89) presents an analysis of his studies on the physiology and pharmacology of the synapse.

The rôle of acetylcholine in synaptic transmission is reviewed by Whitteridge (90). Nachmansohn (91) considers acetylcholine essential for conduction and thinks that it supplies energy to synaptic activity. Welsh suggests that acetylcholine is a coenzyme for one or more enzymes located in or near the cell membranes (92). Lorente de N6 emphasizes that in his experience there is a lack of action of acetylcholine on the whole nerve, but strong action of that compound at nerve terminations (93). By making use of tetraethylammonium chloride (TEAC) Lorente de N6 could reduce conduction velocity of vertebrate nerve to as low as 30 mm. per sec. Kahane & Lévy review choline pharmacology (94).

Roeder describes experiments on a series of anticholinesterases (95). Heymans & Casier (96) study a single one of these, DFP,

and Freedman & Himwich (97) point out that DFP is much more effective when circulated first through the brain. They suggest that its respiratory effects may be mediated at cortical respiratory levels.

Nickerson & Goodman (98), Shaw, Papper & Rovenstine (99) and Grimson, Hendrix & Reardon (100), have studied various adrenergic blocking agents with particular emphasis on dibenamine and its physiological distinction from TEAC. Moe, Caps & Peralta demonstrate action of the latter compound on specific sensory nerve endings (101). The physiological aspects of this drug are investigated by many others (102 to 107).

Patton stimulates the sympathetic chain in cats and records from skin sweat areas a prompt relative negativity (108); even a single shock produces an effect.

Evelyn, Alexander & Cooper present a sobering and thoughtful critique on the clinical results from sympathectomy for hypertension (109). However, the resting arterial pressure may be of less importance than the changes in reflex phenomena following sympathectomy. According to Wilkins, Culbertson & Halperin (110) there is postoperatively a marked decrease or abolition of vasopressor overshooting following depressor procedures. The diminution in reflex vasopressor activity is seen even in patients in whom the resting arterial pressure is not lowered, and it appears to last relatively indefinitely. Thus, the sympathectomized hypertensives may enjoy a reduction in the recurrent vascular pressor stresses following coughing, laughing, changing posture, defecating, etc. Barcroft & Hamilton point out that even though sudomotor and vasomotor reflexes have returned in some sympathectomized limbs after one to two years, vasospastic attacks for which the procedure was done were reduced or absent (111). Chapman & Kinsey (112) report a reduction in resting heart rate and reduced cardiac acceleration following exercise after bilateral thoracic sympathectomy in man.

Walker & Nulsen have succeeded in stimulating the sympathetic chain in man (113). Response to such stimulation is described as a tingling, burning or pricking sensation, which may be referred to a surprisingly localized area. The sensation has not only a long latency, 4 to 20 sec., but it increases to a maximum and then fades away even while stimulation is continued. It may be accompanied by pilomotor activity corresponding to the referred sensory area. The authors suggest that sympathetic stimu-

lation in man may result in activation of afferent nerves as a result of, and secondary to, efferent sympathetic activity.

Knowledge of the synapse and peripheral apparatus of the visceral nervous system has been advanced by Hillarp (114, 115). He demonstrates the morphological constancy and functional unity of the pericellular apparatus, which he considers to be a necessary constituent of a functioning synapse. He is able to produce certain functioning heterogeneous synapses, e.g., between parasympathetic preganglionic and sympathetic postganglionic fibers, and between sympathetic preganglionic fibers and striated muscle. Other heterogeneous combinations fail to form synapses which are functionally or morphologically complete, e.g., the phrenic nerve with sympathetic postganglionic fibers; the hypoglossal nerve with sympathetic postganglionic fibers. Neidle (116) presents evidence that parasympathetic preganglionics in the oculomotor nerve can regenerate, and substitute functionally for, the postganglionics extirpated by removal of the ciliary ganglion.

*Peripheral autonomic apparatus.*—Hillarp (114, 115) shows that the terminal nervous processes which control secretion by the adrenal and submaxillary glands have an intimate relationship to the effector cells and appear to have restricted spheres of influence within the glands. Partial denervation, with time allowed for degeneration of the nerves, followed by electrical excitation of the remaining nerve fibers, results in morphological signs of activity in certain cells adjacent to inactive ones. The borderline is so sharp that the theory of wide diffusion through the gland of a neuroeffector substance is placed in doubt. Each nerve, in fact, appears to have its own particular group of glandular elements and the ensemble constitutes a neuroeffector unit.

Innervation of the thyroid (117), iris (118), capillaries and small vessels (119), development of sensory and motor innervation in the wall of the carotid artery (120) and the fine nervous structures of the heart have been examined (121, 122). Tcheng finds that often sympathetic and parasympathetic fibers pass together to innervate the same cardiac muscle fiber (123).

In a precise study of impulse traffic ascending the vagi from the heart, Jarisch & Zotterman (124) show that slight atrial traction and even normal movements of the heart can cause activation of stretch receptor fibers. Fine fibers carrying impulses from the ventricles give rise to spikes of a different character and are not excited by stretch. It is possible that these represent car-

diac pain fibers. Action currents of sensory nerves conveying impulses from the right and left sides of the heart have been compared (125). Harman finds that the intrinsic nerves in the mouse, rat, cat and primate kidney include fibers which terminate in the juxtaglomerular bodies and have the morphological appearance of sensory neurons (126). There are other fibers terminating in the perivascular spaces of the renal capsule, the renal pelvis, among tubule cells, and in the glomerulus.

Scott reports (127, 128) that individual mesenteric Pacinian corpuscles appear to have continuous fine oscillations of excitability. Gray & Malcolm (129) have succeeded in stimulating such Pacinian corpuscles either mechanically or electrically. Latency of the propagated impulse following mechanical excitation is 0.5 to 1.5 msec. and is independent of stimulus duration. A subthreshold mechanical stimulus can facilitate a subsequent electrical stimulus.

Von Euler is continuing his investigations on the different types of autonomic fibers, and makes three essential distinctions: cholinergic, adrenergic, and histaminergic nerves (130). Folkow and his colleagues present evidence that there are cholinergic vasodilator nerves in the sympathetic outflow to muscles of the hind limb of the cat (131) and dog (132), and that coronary dilator fibers in the dog are cholinergic (133). That stimulation of the stellate ganglion elicits feeble vasomotor tone in the pulmonary arteries has now been demonstrated by Binet & Burnstein (134). This observation is given reinforcement by the exposition of Daly *et al.* (135) concerning pulmonary vasomotor fibers in the sympathetics.

According to Hardenberg & Maloney (139) stimulation of the sympathetic nerves in the extremity brings about a prompt 50 to 100 per cent increase in the quantity of lymph draining the innervated part (139). The authors suggest that there may be a direct action of sympathetic nerves on capillary permeability. However, sympathetic stimulation constricting the precapillary sphincters should increase pressure in the a-v capillaries and so increase fluid for lymph formation.

Goldenberg *et al.* (136), Tullar (137) and Auerbach & Angell (138) have presented evidence that "natural" epinephrine is actually a mixture of norepinephrine and true epinephrine. Epinephrine appears to potentiate sensitivity of cardiac effectors, thus giving an augmentation to effects of acetylcholine and vagal stimulation (140). Similarly, subthreshold and threshold excitation of

the sympathetic nerves potentiate the effects of vagal stimulation (141). On the basis of studying the responses to drugs, Altamirano and his collaborators believe that Cannon's law of denervation should be modified to include a decrease as well as an increase in excitability of denervated structures (142).

Epstein describes the late changes of the peripheral segment of the vagus after vagotomy in man (143). Schachter revives the old claim of Pavlov that there are "secretory inhibitory fibers" in the vagus supply to the stomach and pancreas (144). It is suggested that the vagus supplies a tonic action on pulmonary circulation without which edema is likely to occur (145). On the other hand, bilateral cervical vagotomy is found by Campbell & Visscher to be protective against pulmonary edema subsequent to elevated intracranial pressure (146).

#### VISCERAL REFLEXES

Considerable material covered by this topic has been presented already and is also to be found elsewhere in this volume. Autonomic reflexes in the intact individual cannot be restricted to the ganglionic chain, spinal cord; brain stem, diencephalic or cortical level without special evidence for such restriction. It is probable that, as in somatic motor activity, each level of visceral nervous function adds its contribution to the final reflex effect. As with the somatic motor system, there are many "feed-back mechanisms," which tend to secure visceral homeostasis.

*Reflexes initiated by higher centers.*—Under well controlled conditions, Cranston *et al.* (147) demonstrate the effect of emotions on the arterial pressure response to cold pressor tests in normal individuals. Theron (148) finds a 0.65 correlation between a battery of five physiological variables (pulse volume, rate of change of finger volume during cold pressor test, etc.) and the Bell lability-stability emotion inventory scores of 50 subjects. The emotionally "labile" persons, as identified by the psychological test, have greatly augmented changes in finger volume during simple tasks.

Hinkle & Conger (149) describe increased glycosuria and ketosis in diabetic patients during the course of emotionally charged interviews, with return toward normal on reassurance. Emotional stress in patients with a history of extrasystoles results in many evoked extrasystoles, which are not seen during the control periods or during relaxation following the interviews (150). Zeligs

(151), like Harrington (152), finds that central angioplastic retinopathy can be brought about by combat anxiety. Vasospasm resulting from such anxiety can be seen in retinal vessels in all stages, from transient spastic occlusion to severe permanent retinal lesions due to prolonged spasm. Wolf & Wolff (153) review the relationships between emotions and gastric functions.

*Respiratory reflexes.*—Respiratory rate changes due to changes in bodily posture are mediated by the vagus and are probably basically part of the Hering-Breuer reflex (154). Larrabee & Hodes (155) define cyclic changes in the respiratory centers as they are revealed by the effects of superior laryngeal nerve stimulation. There may be a common mechanism operating on the central decay of inspiratory inhibition and on the decay of afferent stimulatory effect since both decays appear to progress at the same rate.

Hoff & Breckenridge suggest that the medullary respiratory centers are capable of initiating "normal" respiratory activity, and that apneustic breathing is initiated by carotid body receptors acting via the carotid nerve on pontine centers which in turn occlude medullary patterns of breathing (156). Bronchospasm, as measured by intratracheal pressure, whether induced by stimulating the central end of one cut vagus, Hering's nerve, the superior laryngeal nerve, by chemical irritation of the upper respiratory passages, or by artificial pulmonary emboli, always requires an efferent vagal arc (135).

Renshaw, in one of his last investigations, collaborating with Rosenbaum, found that impulses descending each side of the spinal cord from respiratory centers in the cat, have functional distribution to both phrenic motoneurons (157). There is a stronger influence on ipsilateral phrenic activity, but both ipsilateral and "crossed phrenic" activity can be increased or decreased by interfering with or aiding the accomplishment of ventilation. Chatfield & Mead (158, 159) examine the influence of the Hering-Breuer reflex on phrenic "crossing" by means of tracheal occlusion and also by stimulating the vagus with different frequencies. It is probable that whether the "crossed phrenic" phenomenon occurs or not depends upon the level of activity of the respiratory centers.

*Vascular reflexes.*—The cardiodepressor reflex elicited from the heart involves activation of very thin afferent fibers with terminations in the atria and ventricles, whereas larger afferent fibers ending in the atrial region may have a separate reflex rôle, such as taking part in the Bainbridge reflex (125). Clamping a branch of

the pulmonary artery gives rise to systemic vasoconstriction, a reflex not dependent upon an intact vagus and possibly initiated by activity of pressure receptors in the pulmonary vascular bed (160). The vasopressor reflex, initiated after a latency of several seconds following excitation of the peripheral portion of the cut vagus (161), involves both higher centers and the stellate ganglion, according to von Euler (162). Liljestrand offers an experimental exposition of the opposite hemodynamic responses of the pulmonary and systemic vessels during various conditions of available respiratory gases and tissue needs (163). Lack of oxygen in the periphery, for example, is followed by local vasodilatation, whereas when it occurs in the pulmonary bed, by local vasoconstriction. This is but one example of many apparently teleological mechanisms.

Streiff (164) notes acute circulatory disorders in the retinal vessels in cases of hyperexcitability of the carotid sinus. Sarnoff, Hardenbergh & Whittenberger outline the mechanisms of arterial pressure response to the Valsalva test and use that test as an indicator of the intactness of sympathetic outflow (165).

Up to a critical point, the greater the depression of respiratory centers by anoxemia, the longer the period of apnea following reapplication of oxygen, according to Grandpierre (166). Reflex excitability of respiration is preserved during this apneic period.

Aviado & Pontius (167) have introduced veratridine into the peripheral branches of the pulmonary artery on one side and caused effects which appear to arise from chemoreceptors in the lungs and which have reflex actions opposite to those produced by the same drug acting on carotid sinus receptors.

Heymans (168) reviews the rôle of pressure and chemoreceptors in regulation of respiration and circulation. Eckstein *et al.* (169) point out that stimulation of the acceleratory nerves to the heart in the presence of artificial reduction of cardiac work still effects an increase in oxygen consumption, and therefore must produce decreased efficiency. Duration of bradycardia following reapplication of oxygen to an anoxic animal is a function of the intensity of the anoxia and is mediated by the vagus (170).

Hypothermia may evoke reflex cardiac acceleration in dogs until the temperature reaches 19°C. at which time the mechanism appears to fail (171). What I take to be an analogous reflex break occurs in the guinea pig at 23°C. (172).

Taylor & Page (173) argue that renal vasoconstriction follow-

ing lower limb tourniquet shock not only has a nervous pathway which can be blocked by cord transection at L1, but that there is also a humoral effect since a denervated kidney is also somewhat affected [Cf. also Koella (56)]. Cerletti, Bircher & Rothlin (174) find that hydergin successfully blocks both the humoral and nervous factors and therefore probably acts on the effector organs. According to Little and co-workers (175), carbon dioxide administration to humans results in a renal vasoconstriction which begins and ends promptly. Black & Sanders (176) caution against indiscriminate use of the term "Oxford shunt mechanism" in diverse clinical conditions without providing critical means of recognizing when the shunt is active in man.

Kramer & Schulze (177) discuss peripheral and central vegetative nerve influences on blood vessels of the skin.

Bouckaert & Jourdan (178) review cerebral circulation. Kety and his team have published a remarkable series of communications on human cerebral circulation during various physiological and pathological states (179 to 183) and it is now abundantly clear that cerebral vasospasm accompanies many diseases.

*Gastrointestinal reflexes.*—Evans (184) considers some problems of enteric innervation. According to Bozler (185) the myenteric reflex in the rabbit and dog, elicited by mechanical or electrical stimulation, or by the application of acetylcholine, is evidenced by a pronounced annular contraction at the oral side of the applied stimulation. This constrictive response can be prevented by synapse-blocking drugs, which presumably act on the intrinsic nerves. The reflex is not propagated, but is thought to be continually reactivated by mechanical stimulation of descending intestinal contents, which act successively on more caudal structures.

Extrinsic innervation of the stomach has been investigated by Bekaert (186), Jourdan & Collet (187), Inberg (188) and Kahlson (189). Bekaert indicates that stimulation of the accessory nerve at its origin produces relaxation of the stomach. Stimulation of the superior cervical ganglion was without effect, whereas excitation of the vagus gave forceful contractions of the stomach. Cutting dorsal roots from T6 to 12 abolishes the respiratory and the immediate vascular reflex response to gastric distension in the chloralosed cat (188).

A difference between the effect of tetraethylammonium chloride on dog and man in respect to gastrointestinal motility is found by

Lane *et al.* (190). In the dog, Jourdan finds that the pyloric sphincter is narrowly dependent upon vagus and sympathetic balances and that cutting the vagus leads to relative pylorospasm (187). Epinephrine inhibits pyloric motility and increases pyloric tone (191). Pyloric contractions in man occur at the rate of about 11 per min. and pressure and rhythm patterns are different from those of the stomach and intestines (192). Wener & Hoff (193) present an excellent review of the physiology of peptic ulcer formation and underline therapeutic rationale. Their reprint, but not the published version, has a bibliography.

Mechanical filling of the stomach initiates afferent impulses in dogs which are partial clues in gauging the amount of water drunk (194). Janowitz & Grossman (195) find that food intake in dogs is regulated both by the presence of food in the mouth and by distension of the stomach, and that both factors must act together to obtain "normal intake" behavior. Sham feeding in dogs can induce or inhibit gastric motility, depending upon the basal state of gastric activity (196). Histamine provocation of gastric pepsin secretion depends upon pre-existing or combined cholinergic stimulation, according to Stavsky (197). Brücke has studied the motility of the gall bladder (198).

Mechanical stimulation of the duodenum brings about a change in rate of pancreatic exocrine secretion (199). Reflex inhibition of pancreatic flow brought about by faradization of the mesenteric nerves, or more effectively by inflation of the intestines, can occur even though the vagus and splanchnic nerves are sectioned. Kuntz & Richins suggest that there is a direct inhibitory reflex mediated through the celiac ganglion (200).

Abdominal cutaneous stimulation affects circulation in the duodenal arterioles and capillary bed. Cutaneous warming leads to dilatation of duodenal vessels, whereas application of cold leads to vasoconstriction (201). By injecting a small quantity of distilled water in the cutaneous area of referred pain, Doret is able to relieve ulcer pain and simultaneously diminish the force of gastrointestinal contractions (202).

*Miscellaneous reflexes.*—Brierley & Field (203), in tracing the fate of intraneurally injected radioactive substances, came across an important observation resembling "mirror image" effects. Reflex phenomena, arising in the region of nerve damaged by the injection, initiated a localized change in blood-nerve relationship which is highly suggestive of an increased ion exchange taking

place in the mirror image segment of nerve on the side of the body opposite the traumatized point. The authors call attention to the resemblance of this phenomenon to the arterial spasm described by Barnes & Trueta (204) as occurring occasionally in the limb opposite an applied tourniquet. It is clear that in both circumstances, some localized change in physiology is brought about reflexly, and that it involves centers at least as high as the spinal cord. Szentágothai (205) makes the important observation that all vegetative reflexes in which the nervous system is involved consist of at least four neurons.

#### RECENT MONOGRAPHS

Bovet & Bovet-Nitti provide a scholarly treatise on the chemistry, pharmacology and physiology of drugs affecting the visceral nervous system (206). It is well organized, extremely thorough in fundamentals, and presents interesting evidence on the sites of action of different pharmaceutical preparations.

Tardieu & Tardieu present an outline of the anatomy, physiology and pharmacology of the visceral nervous system (207). Their presentation is didactic and presents the anatomy as though little or no progress had been made since the time of Langley. The best sections of the book describe physiological and pathological responses of visceral tissues to drugs, toxins etc. applied to sympathetic ganglia.

Hess has published two works summarizing about thirty years of investigation on the functional organization of the visceral nervous system with particular reference to the diencephalon (26, 27). His books are abundantly illustrated and the captions are given in English as well as German. Several thousand experiments, involving stimulation of the free moving and unanesthetized cat by means of fine preplanted electrodes, are comprehensively presented in charts illustrating an anatomical representation of somatic and visceral motor functions. Responses are documented by cinematographic and kymographic recording and the region stimulated is painstakingly controlled histologically.

Morin's textbook of nervous system physiology (208), and the monograph of Ajuriaguerra & Hécaen on the cerebral cortex (209) contribute little new information, but summarize present concepts excellently.

Kuntz's chapter in the 1948 *Progress in Neurology and Psychiatry* (210) provides an excellent review of visceral nervous function.

Fulton's new third edition of *Physiology of the Nervous System* (211) has been largely rewritten and there is much new material on autonomic mechanisms and their integration with other nervous activity. Fulton's Withering Lecture Series (212) present a scholarly, brief, but lively exposition of the rôle of the frontal lobes in the visceral functions of the nervous system.

#### ADDENDUM

The author has requested that attention be called to the publication of a book by Reilly and co-workers<sup>3</sup> concerning nervous mechanisms in the production of renal lesions. Various procedures (electrical stimulation of the splanchnic and other visceral nerves, injection of typhoid toxin, potassium cantharidine, etc.) caused within a few hours albuminuria, hematuria, and sometimes azotemia. Chronic denervation of the kidney prevented these disorders which were attributed to reflex constriction of renal vessels. Single episodes of sympathetic nervous activation produced disturbances from which the kidneys ordinarily recover completely. Repetition of stimulation, by causing persistent vasoconstriction, evoked glomerular lesions (edema, hyalinization, and fibrosis) which may result in grave permanent injury to the kidney. The possible rôle of such renal crises in the pathogenesis of the chronic nephritides of man is discussed. The author, in collaboration with Dr. Reilly, is preparing an extensive English summary of this most important work.

#### LITERATURE CITED

1. HOAGLAND, H., *Science*, **109**, 157-64 (1949); FESSARD, A., *L'année psychologique*, **32**, 49-117 (1932)
2. YAKOVLEV, P. I., *J. Nervous Mental Diseases*, **107**, 313-35 (1948)
3. BARD, P., AND MOUNTCASTLE, V. B., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 362-404 (1948)
4. SMITH, W. K., *Trans., Am. Neurol. Assoc.* (In press)
5. WARD, A. A., JR., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 438-45 (1948)
6. LIVINGSTON, R. B., FULTON, J. F., DELGADO, J. M. R., SACHS, E., JR., BRENDLER, S. J., AND DAVIS, G. D., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 405-20 (1948)
7. MEYER, A., AND McLARDY, T., *J. Mental Sci.*, **94**, 555-64 (1948); EGAN, G., *J. Mental Sci.*, **95**, 115-23 (1949)
8. NETSKY, M. G., AND STARR, H., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 610-41 (1947)

<sup>3</sup> Reilly, J., Compagnon, A., Laporte, A., and DuBruit, H., *Le rôle du système nerveux en pathologie rénale*, 112 pp. (Masson, Paris, 1942).

9. REITMAN, F., *Brit. Med. J.*, **2**, 1064 (1948)
10. SWEET, W. H., COTZIAS, G. C., SEED, J., AND YAKOVLEV, P. I., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 795-822 (1948)
11. KAADA, B. R., PRIBRAM, K. H., AND EPSTEIN, J. A., *Federation Proc.*, **8**, 83-84 (1949); *J. Neurophysiol.*, **12**, 347-56 (1949)
12. FULTON, J. F., PRIBRAM, K. H., STEVENSON, J. A. F., AND WALL, P., *Trans., Am. Neurol. Assoc.* (In press)
13. POOL, J. L., AND RANSOHOFF, J., *Trans., Am. Neurol. Assoc.* (In press)
14. SACHS, E., JR., BRENDLER, S. J., AND FULTON, J. F., *Brain*, **72**, 227-40 (1949)
15. LIVINGSTON, R. B., CHAPMAN, W. P., LIVINGSTON, K. E., AND KRAINTZ, L., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 421-32 (1948)
16. CHAPMAN, W. P., LIVINGSTON, R. B., AND LIVINGSTON, K. E., *J. Clin. Invest.*, **27**, 529 (1948)
17. ALLEN, W. F., *J. Comp. Neurol.*, **88**, 425-38 (1948)
18. DELGADO, J. M. R., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 435-37 (1948)
19. HOFF, E. C., KELL, J. F., JR., HASTINGS, N., GRAY, E. H., AND SHOLES, D. M., *Federation Proc.*, **8**, 76 (1949)
20. CORT, J. H., AND BARRON, D. H., *Federation Proc.*, **7**, 15 (1948)
21. JÖGI, P., STRÖM, G., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 212-21 (1949)
22. STRÖM, G., AND UVNÄS, B., *Acta Physiol. Scand.*, **16**, Suppl. 53, 59-60 (1948)
23. DAVY, L. S., AND FULTON, J. F., *Research Pubs., Assoc. Research Nervous Mental Disease* (In press); FULTON, J. F., *Functional Localization in the Frontal Lobes and Cerebellum*, 140 pp. (Clarendon Press, London, 1949)
24. MOSINGER, M., *Arch. suisse neurol. psychiat.* (In press)
25. HAYNE, R., MEYERS, R., AND KNOTT, J. R., *J. Neurophysiol.*, **12**, 185-95 (1949)
26. HESS, W. R., *Die funktionelle Organisation des vegetativen Nervensystems*, 226 pp. (Schwabe, Basel, 1948)
27. HESS, W. R., *Das Zwischenhirn; Syndrome, Lokalisationen, Funktionen*, 187 pp. (Schwabe, Basel, 1949)
28. McCULLOCH, W. S., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 95-105 (1948)
29. METTLER, F. A., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 162-99 (1948)
30. ROSE, J. E., AND WOOLSEY, C. N., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 210-32 (1948)
31. ROSE, J. E., AND WOOLSEY, C. N., *J. Comp. Neurol.*, **89**, 279-347 (1948)
32. VON BONIN, G., AND GREEN, J. R., *J. Comp. Neurol.*, **90**, 243-54 (1949)
33. MINKOWSKI, M., *IVe Congrès neurologique international*, **2**, 22 (Paris, September, 1949)
34. McLARDY, T., *Brain*, **71**, 290-303 (1948)
35. FREEMAN, W., AND WATTS, J. W., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 200-9 (1948)
36. LE GROS CLARK, W. E., *IVe Congrès neurologique international*, 49-52 (Paris, September, 1949)
37. SPIEGEL, E. A., WYCIS, H. T., AND FISCHER, K. H., *Trans. Am. Neurol. Assoc.* (In press)

38. BUCHANAN, A. R., AND HILL, R. M., *Proc. Soc. Exptl. Biol. Med.*, **71**, 126-29 (1949)
39. LUNDBAEK, K., *Ugeskrift Laeger*, **110**, 825-33 (1948)
40. BROBECK, J. R., *Yale J. Biol. Med.*, **20**, 545-52 (1948)
41. ROBBARD, S., *Science*, **108**, 413-15 (1948)
42. BONVALLET, M., DELL, P., AND STUTINSKY, F. S., *Arch. intern. physiol.*, **54**, 273-91 (1949)
43. BONVALLET, M., DELL, P., STUTINSKY, F. S., AND BEAUVALLET, M., *Compt. rend. soc. biol.*, **142**, 937-41 (1948)
44. STUTINSKY, F., *Compt. rend. soc. biol.*, **143**, 195-98 (1949)
45. JANOWITZ, H. D., HANSON, M. E., AND GROSSMAN, M. I., *Am. J. Physiol.*, **156**, 87-91 (1949)
46. ARCHDEACON, J. W., PRESNELL, M. W., AND WALTER, C. J., *Am. J. Physiol.*, **157**, 149-52 (1949)
47. HARRIS, G. W., *J. Physiol. (London)*, **107**, 412-17 (1948)
48. HARRIS, G. W., *J. Physiol. (London)*, **107**, 418-29 (1948)
49. HARRIS, G. W., *Proc. Roy. Soc. Med.*, **41**, 661-66 (1948)
50. HILLARP, N. A., *Acta Endocrinol.*, **2**, 33-43 (1949)
51. O'CONNOR, W. J., *Proc. Roy. Soc. Med.*, **41**, 666-70 (1948)
52. FOLKOW, B., STRÖM, G., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 317-26 (1949)
53. ABRAMS, M., DEFRIEZ, A. I. C., TOSTESON, D. C., AND LANDIS, E. M., *Am. J. Physiol.*, **156**, 233-47 (1949)
54. KELLER, A. D., *Am. J. Physiol.*, **154**, 82-86 (1948)
55. FOLKOW, B., STRÖM, G., AND UVNÄS, B., *Acta Physiol. Scand.*, **17**, 327-38 (1949)
56. KOELLA, W., *Helv. Physiol. et Pharmacol. Acta*, **7**, C12-13 (1949)
57. SAWYER, C. H., MARKEE, J. E., AND TOWNSEND, B. F., *Endocrinology*, **44**, 18-37 (1949)
58. EVERETT, J. W., SAWYER, C. H., AND MARKEE, J. E., *Endocrinology*, **44**, 234-50 (1949)
59. BONVALLET, M., DELL, P., AND STUTINSKY, F., *Compt. rend. soc. biol.*, **143**, 80-82 (1949)
60. BENDER, M. B., FURLOW, L. T., AND TEUBER, H. L., *Confinia Neurol.*, **9**, 140-57 (1949)
61. SCHACHTER, M., AND SCHACHTER, R., *Can. Med. Assoc. J.*, **60**, 607-9 (1949)
62. FUNKENSTEIN, D. H., GREENBLATT, M., AND SOLOMON, H. C., *J. Nervous Mental Disease*, **108**, 409-22 (1948)
63. KERSCHMAN, J., *J. Neurol. Neurosurg. Psychiat.*, **12**, 25-33 (1949)
64. CAVENESS, W., *Trans. Am. Neurol. Assoc.* (In press)
65. KLEITMAN, N., *Physiol. Revs.*, **29**, 1-30 (1949)
66. HESS, W. R., *J. physiol.*, **41**, 61A-7A (1949)
67. KAYSER, C., *J. physiol.*, **41**, 1A-53A (1949)
68. BORISON, H. L., AND WANG, C. S., *Federation Proc.*, **8**, 13 (1949)
69. ESSIG, C. F., HAMPSON, J. L., BALES, P. D., AND HIMWICH, H. E., *Trans. Am. Neurol. Assoc.* (In press)
70. ATKINSON, W. J., *J. Neurol. Neurosurg. Psychiat.*, **12**, 137-51 (1949)
71. GERNANDT, B., *J. Neurophysiol.*, **12**, 173-84 (1949)
72. BONVALLET, M., AND DELL, P., *Compt. rend. soc. biol.*, **142**, 132-35 (1948)

73. HALL, V. E., ATTARDO, F. P., AND PERRYMAN, J. H., *Proc. Soc. Exptl. Biol. Med.*, **69**, 413-15 (1948)
74. GETZ, B., AND SIRIUS, T., *J. Comp. Neurol.*, **90**, 95-110 (1949)
75. THOMPSON, C. E., AND WITHAM, A. C., *N. Engl. J. Med.*, **239**, 291-94 (1948)
76. POLLOCK, L. J., BOSHER, B., CHOR, H., FINKELMAN, I., ARIEFF, A. J., AND BROWN, M., *Trans. Am. Neurol. Assoc.* (in press)
77. SCHUMACHER, G. A., GUTHRIE, T. C., ROBERTSON, H. S., AND WOLFF, H. G., *Trans. Am. Neurol. Assoc.* (in press)
78. MUNRO, D., HORNE, H. W., JR., AND PAULL, D. P., *N. Engl. J. Med.*, **239**, 903-11 (1948)
79. HORNE, H. W., PAULL, D. P., AND MUNRO, D., *N. Engl. J. Med.*, **239**, 959-61 (1948)
80. ALBERT, R. E., AND PALMES, E. D., *Federation Proc.*, **8**, 1-2 (1949)
81. MALMÉJAC, J., CHARDON, G., AND GROSS, A., *Compt. rend. soc. biol.*, **142**, 1102-4 (1948)
82. EMMELIN, N. G., AND MACINTOSH, F. C., *Acta Physiol. Scand.*, **16**, Suppl. 53, 17-18 (1948)
83. LORENTE DE NÓ, R., AND LAPORTE, Y., *Comptes Rendus du Colloque International d'Electrophysiologie*, 2 v. (Centre National de la Recherche Scientifique, Paris, 1950)
84. BULLOCK, T. H., *J. Neurophysiol.*, **11**, 343-64 (1948)
85. WIERSMA, C. A. G., AND SCHALLEK, W., *J. Neurophysiol.*, **11**, 491-96 (1948)
86. POSTERNAK, J. M., AND LARRABEE, M. G., *Am. J. Med. Sci.*, **215**, 353-54 (1948)
87. POSTERNAK, J. M., AND LARRABEE, M. G., *Helv. Physiol. et Pharmacol. Acta*, **6**, C62 (1948)
88. SAUNDERS, J. W., AND SINCLAIR, J. D., *J. Neurophysiol.*, **12**, 217-24 (1949)
89. MARRAZZI, A. S., *Bull. School Med. Univ. Maryland*, **33**, 154-62 (1949)
90. WHITTERIDGE, D., *J. Neurol. Neurosurg. Psychiat.*, **11**, 134-40 (1948)
91. NACHMANSOHN, D., *Bull. Johns Hopkins Hosp.*, **83**, 463-91 (1948)
92. WELSH, J. H., *Bull. Johns Hopkins Hosp.*, **83**, 568-86 (1948)
93. LORENTE DE NÓ, R., *Bull. Johns Hopkins Hosp.*, **83**, 497-506 (1948)
94. KAHANE, E., AND LÉVY, J., *J. physiol.*, **41**, 183-233 (1949)
95. ROEDER, K. D., *Bull. Johns Hopkins Hosp.*, **83**, 587-603 (1948)
96. HEYMANS, C., AND CASIER, H., *Arch. intern. pharmacodynamie*, **77**, 64-66 (1948)
97. FREEDMAN, A. M., AND HIMWICH, H. E., *Am. J. Physiol.*, **156**, 125-28 (1949)
98. NICKERSON, M., AND GOODMAN, L. S., *Federation Proc.*, **7**, 397-409 (1949)
99. SHAW, W. M., PAPPER, E. M., AND ROVENSTINE, E. A., *J. Lab. Clin. Med.*, **34**, 669-73 (1949)
100. GRIMSON, K. S., HENDRIX, J. P., AND REARDON, M. J., *J. Am. Med. Assoc.*, **138**, 154 (1948)
101. MOE, G. K., CAPO, L. R., AND PERALTA, R. B., *Am. J. Physiol.*, **153**, 601-5 (1948)
102. POSEY, E. L., JR., BROWN, H. S., AND BARGEN, J. A., *Gastroenterology*, **11**, 83-89 (1948)
103. PAGE, I. H., PRINCE, R., AND REINHARD, J. J., JR., *Federation Proc.*, **8**, 122-23 (1949)
104. AAS, K., AND BLEGEN, E., *Lancet*, **1**, 999-1001 (1949)
105. LIAN, C., HAMET, R., AND BERGAMO, G., *Semaine hôp.* (Paris), **24**, 2235-43 (1948)

106. ZWEIG, M., STEIGMANN, F., AND MEYER, K. A., *Gastroenterology*, **11**, 200-7 (1948)
107. GROB, D., HARVEY, A. M., AND HALADAY, D. A., *Bull. Johns Hopkins Hosp.*, **84**, 279-82 (1949)
108. PATTON, H. D., *J. Neurophysiol.*, **11**, 217-27 (1948)
109. EVELYN, K. A., ALEXANDER, F., AND COOPER, S. R., *J. Am. Med. Assoc.*, **140**, 592-600 (1949)
110. WILKINS, R. W., CULBERTSON, J. W., AND HALPERIN, M. H., *Ann. Internal Med.*, **34**, 291-306 (1949)
111. BARCROFT, H., AND HAMILTON, G. T. C., *Lancet*, **II**, 770 (1948)
112. CHAPMAN, E. M., KINSEY, D., CHAPMAN, W. P., AND SMITHWICK, R. H., *J. Am. Med. Assoc.*, **137**, 579-84 (1948)
113. WALKER, E. A., AND NULSEN, F., *Arch. Neurol. Psychiat.*, **59**, 559-60 (1948)
114. HILLARP, N. A., *Acta Anat.*, **2**, Suppl. 4, 1-153 (1946)
115. HILLARP, N. A., *Acta Physiol. Scand.*, **17**, 120-29 (1949)
116. NEIDLE, E. A., *Federation Proc.*, **8**, 117-18 (1949)
117. BÖLÖNYI, F., *Acta Anat.*, **5**, 306-10 (1948)
118. HINSHAW, J. R., *J. Anat.*, **83**, 75 (1949)
119. NELEMANS, F. A., *Am. J. Anat.*, **83**, 43-66 (1948)
120. BONARD, E. C., *Compt. rend. soc. biol.*, **142**, 1415-16 (1948)
121. MEYLING, H. A., *J. Anat.*, **83**, 66 (1949)
122. CONTI, G., *Acta Anat.*, **5**, 255-90 (1948)
123. TCHENG, K. T. (Unpublished data)
124. JARISCH, A., AND ZOTTERMAN, Y., *Acta Physiol. Scand.*, **16**, 31-51 (1949)
125. KAINDL, F., POLZER, K., AND SCHOBER, W., *Arch. intern. pharmacodynamie*, **77**, 256-69 (1948)
126. HARMAN, P. J., AND DAVISS, H., *J. Comp. Neurol.*, **89**, 225-43 (1948)
127. SCOTT, D., JR., *Federation Proc.*, **8**, 142 (1949)
128. SCOTT, D., JR., *Am. J. Med. Sci.*, **217**, 355 (1949)
129. GRAY, J. A. B., AND MALCOLM, J. L., *Proc. Roy. Soc. (London) [B]* (In press)
130. EULER, U. S. V., *Acta Physiol. Scand.*, **16**, Suppl. 53, 20-21 (1948)
131. FOLKOW, B., AND ÜVNÄS, B., *Acta Physiol. Scand.*, **15**, 365-88 (1949)
132. FOLKOW, B., FROST, J., HAEGER, K., AND ÜVNÄS, B., *Acta Physiol. Scand.*, **17**, 195-200 (1949)
133. FOLKOW, B., FROST, J., AND ÜVNÄS, B., *Acta Physiol. Scand.*, **17**, 201-5 (1949)
134. BINET, L., AND BURNSTEIN, M., *J. français méd. chirurg. thoraciques*, **2**, 101-22 (1948)
135. DALY, I. DE B., DUKE, H., HEBB, C. O., AND WEATHERALL, J., *Quart. J. Exptl. Physiol.*, **34**, 285-313 (1948)
136. GOLDENBERG, M., FABER, M., ALSTON, E. J., AND CHARGOFF, E. C., *Science*, **109**, 534-35 (1949)
137. TULLAR, B. F., *Science*, **109**, 536-37 (1949)
138. AUERBACH, M. E., AND ANGELL, E., *Science*, **109**, 537-38 (1949)
139. HARDENBERGH, E., AND MALONEY, J. V., JR., *Federation Proc.*, **8**, 67 (1949)
140. MIDDLETON, S., AND TALESNIK, J., *Federation Proc.*, **8**, 110 (1949)
141. MIDDLETON, S., AND TALESNIK, J., *Federation Proc.*, **8**, 110-11 (1949)
142. ALTAMIRANO, M., FERNÁNDEZ, D., AND LUCO, J. V., *Am. J. Physiol.*, **156**, 280-84 (1949)

143. EPSTEIN, J. A., *J. Mt. Sinai Hosp. N. Y.*, **15**, 83-89 (1948)
144. SCHACHTER, M., *Am. J. Physiol.*, **156**, 248-55 (1949)
145. JOURDAN, F., FINAS, C., AND COLLET, A., *Compt. rend. soc. biol.*, **142**, 1127-29 (1948)
146. CAMPBELL, G. S., AND VISSCHER, M. B., *Am. J. Physiol.*, **157**, 130-34 (1949)
147. CRANSTON, R. W., CHALMERS, J. H., TAYLOR, H. L., HENSCHER, A., AND KEYS, A., *Federation Proc.*, **8**, 30 (1949)
148. THERON, P. A., *Psychosomat. Med.*, **10**, 335-46 (1949)
149. HINKLE, L. E., JR., AND CONGER, G. T., *Federation Proc.*, **8**, 75-76 (1949)
150. STEVENSON, I. P., DUNCAN, C. H., AND WOLF, S., *Bull. N. Y. Acad. Med.*, **24**, 393 (1948)
151. ZELIGS, M. A., *Psychosomat. Med.*, **10**, 110-17 (1949)
152. HARRINGTON, D. O., *J. Am. Med. Assoc.*, **133**, 669-71 (1947)
153. WOLF, S., AND WOLFF, H. G., *Am. Practitioner*, **3**, 1-14 (1948)
154. REED, E. A., AND SCOTT, J. C., *Federation Proc.*, **8**, 130-31 (1949)
155. LARRABEE, M. G., AND HODES, R., *Am. J. Physiol.*, **155**, 147-64 (1948)
156. HOFF, H. E., AND BRECKENRIDGE, C. G., *Federation Proc.*, **8**, 76 (1949)
157. ROSENBAUM, H., AND RENSHAW, B., *Am. J. Physiol.*, **157**, 468-76 (1949)
158. CHATFIELD, P. O., AND MEAD, S., *Federation Proc.*, **7**, 20 (1948)
159. CHATFIELD, P. O., AND MEAD, S., *Am. J. Physiol.*, **154**, 417-22 (1948)
160. DONNET, V., ZWIRN, P., PRUNEYRE, A., AND MAFFRE, S., *Compt. rend. soc. biol.*, **143**, 88-91 (1949)
161. BINET, L., AND BURNSTEIN, M., *Compt. rend. soc. biol.*, **142**, 603-6 (1948)
162. EULER, C. v., *Acta Physiol. Scand.*, **16**, Suppl. 53, 19-20 (1948)
163. LILJESTRAND, G., *Semaine hôp. (Paris)*, **24**, 1679-84 (1948)
164. STREIFF, E. B., *Bull. Schweiz. Akad. Med. Wissensch.*, **5**, 49-54 (1949)
165. SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L., *Am. J. Physiol.*, **154**, 316-27 (1948)
166. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *Compt. rend. soc. biol.*, **142**, 1028-29 (1948)
167. AVIADO, D. M., AND PONTIUS, R. G., *Federation Proc.*, **8**, 5-6 (1949)
168. HEYMANS, C., *Bull. Schweiz. Akad. Med. Wissensch.*, **4**, 77-87 (1948)
169. ECKSTEIN, R. W., STROUD, M., DOWLING, C. V., ECKEL, R., AND PRITCHARD, W. H., *Federation Proc.*, **8**, 38-39 (1949)
170. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *Compt. rend. soc. biol.*, **142**, 1030-31 (1948)
171. HEGNAUER, A. H., AND HATERIUS, H. O., *Federation Proc.*, **8**, 71 (1949)
172. GOSSELIN, R. E., *Am. J. Physiol.*, **157**, 103-15 (1949)
173. TAYLOR, R. D., AND PAGE, I. H., *Federation Proc.*, **8**, 155 (1949)
174. CERLETTI, A., BIRCHER, R., AND ROTHLIN, E., *Helv. Physiol. et Pharmacol. Acta*, **7**, C7-8 (1949)
175. LITTLE, W. J., AVERA, J. W., AND HOOBLER, S. W., *Federation Proc.*, **8**, 98-99 (1949)
176. BLACK, D. A. K., AND SAUNDERS, M. G., *Lancet*, **1**, 733-74 (1949)
177. KRAMER, K., AND SCHULZE, W., *Arch. ges., Physiol. (Pflügers)*, **250**, 142-70 (1948)
178. BOUCKAERT, J. J., AND JOURDAN, F., *J. physiol.*, **41**, 69A-114A (1949)
179. SHENKIN, H. A., SCHEUERMAN, W. G., SPITZ, E. B., AND GROFF, R. A., *Am. J. Med. Sci.*, **216**, 714-15 (1948)

180. KETY, S. S., KING, B. D., HAFKENSCHIEL, J. H., HORVATH, S. M., AND JEFFERS, W. A., *J. Clin. Invest.*, **27**, 543 (1948)
181. SHENKIN, H. A., AND YASKIN, J. C., *Trans. Am. Neurol. Assoc.* (In press)
182. SHENKIN, H. A., WOODFORD, R. B., FREYHAN, F. A., AND KETY, S. S., *Research Pubs., Assoc. Research Nervous Mental Disease*, **27**, 823-31 (1948)
183. HARMEL, M. H., HAFKENSCHIEL, J. H., AUSTIN, G. M., CRUMPTON, C. W., AND KETY, S. S., *J. Clin. Invest.*, **28**, 415-18 (1949)
184. EVANS, D. H. L., *J. Anat.*, **83**, 59 (1949)
185. BOZLER, E., *Am. J. Physiol.*, **157**, 329-37 (1949)
186. BEKAERT, J., *Experientia*, **5**, 246 (1949)
187. JOURDAN, F., AND COLLET, A., *Compt. rend. soc. biol.*, **143**, 279-80 (1949)
188. INBERG, K. R., *Acta Physiol. Scand.*, **18**, 36-50 (1949)
189. KAHLSON, G., *Brit. Med. J.*, **II**, 1091-95 (1948)
190. LANE, A., ROBERTSON, C. R., AND GROSSMAN, M. I., *Federation Proc.*, **8**, 91 (1949)
191. LOUCKES, H., BRODY, D. A., AND QUIGLEY, J. P., *Federation Proc.*, **8**, 100 (1949)
192. STEGGERDA, F. R., AND CLARK, W. C., *Federation Proc.*, **8**, 151 (1949)
193. WENER, J., AND HOFF, H. E., *Can. Med. Assoc. J.*, **59**, 115-40 (1948)
194. TONBIN, E. J., *Federation Proc.*, **8**, 158 (1949)
195. JANOWITZ, H. D., AND GROSSMAN, M. I., *Federation Proc.*, **8**, 81 (1949)
196. LORBER, S. H., KOMAROV, S. A., AND SHAY, H., *Federation Proc.*, **8**, 99 (1949)
197. STAVRAKY, G. W., *Federation Proc.*, **8**, 151 (1949)
198. BRÜCKE, H., *Wien. klin. Wochschr.*, **61**, 241-44 (1949)
199. WALDRON, J. M., THOMAS, J. E., AND TKACZ, L. P., *Federation Proc.*, **8**, 161 (1949)
200. KUNTZ, A., AND RICHINS, C. A., *J. Neurophysiol.*, **12**, 29-35 (1949)
201. RICHINS, C. A., AND BRIZZEE, K., *J. Neurophysiol.*, **12**, 131-36 (1949)
202. DORET, J. P., *Rev. méd. Suisse romande*, **69**, 758-65 (1949)
203. BRIERLEY, J. B., AND FIELD, E. J., *J. Neurol. Neurosurg. Psychiat.*, **12**, 86-99 (1949)
204. BARNES, J., AND TRUETA, J., *Brit. J. Surg.*, **30**, 74-79 (1942)
205. SZENTÁGOTHAI, J., *J. Neurophysiol.*, **11**, 445-54 (1948)
206. BOVET, D., AND BOVET-NITTI, F., *Structure et activité pharmacodynamique des médicaments du système nerveux végétatif*, 832 pp. (Masson, Paris, 1948)
207. TARDIEU, G., AND TARDIEU, C., *Le système nerveux végétatif*, 742 pp. (Masson, Paris, 1948)
208. MORIN, G., *Physiologie du système nerveux central*, 270 pp. (Masson, Paris, 1948)
209. AJURIAGUERRA, J. DE, AND HÉCAEN, H., *Le cortex cérébral: étude neuro-psycho-pathologique*, 413 pp. (Masson, Paris, 1949)
210. KUNTZ, A., *Progress in Neurology and Psychiatry*, **3**, 207-42 (Grune & Stratton, Inc., New York, 1948)
211. FULTON, J. F. *Physiology of the Nervous System*, 3rd Ed., 667 pp. (Oxford Univ. Press, New York, 1949)
212. FULTON, J. F., *Functional Localization in the Frontal Lobes and Cerebellum*, 140 pp. (Clarendon Press, Oxford, 1949)
213. HENNEMAN, E., *Trans. Am. Neurol. Assoc.*, **73**, 150-53 (1948)

## PHYSIOLOGY OF SMELL AND TASTE

BY HARRY D. PATTON

*Department of Physiology and Biophysics, University of Washington  
School of Medicine, Seattle, Washington*

Rightly or wrongly, the physiologist is often primarily concerned with those systems most vital to the welfare of the organism. Taste and smell are considered luxury senses, hedonically useful, but bioeconomically dispensable. Moreover, both present singular difficulties to the experimenter; the olfactory end organs defy ready access, gustatory impulses reach the brain through a multiple rather than a single path, and for neither taste nor smell can the physical strength of the stimulus be controlled in the precise manner which characterizes studies of vision and audition. Accordingly, studies of taste and smell are relatively few and have not been fully reviewed in a previous *Annual Review of Physiology*, whereas vision and audition have been reviewed five and three times, respectively. Pfaffman's (1) and Adrian's studies (2, 3) of single gustatory and olfactory units have proved that the "chemical senses" can, with some limitations, be approached by classical sense organ techniques, and Richter's demonstration (4) of the role of taste in self-selection of diets has brought to light a hitherto unsuspected importance of this modality. There is, thus, hope that taste and smell will come into their own as respectable special senses.

This is primarily a review of papers appearing between July 1945 and June 1949, but since the subject has not previously been reviewed here, the author has not hesitated to mention briefly earlier papers bearing directly on current problems. For a full treatment of the subject, Moncrieff's monograph (5) is recommended. Since Dethier and Chadwick (6) recently reviewed the chemoreceptor mechanisms in insects, the present review is confined to studies of vertebrates.

### TASTE

*Thresholds.*—Taste thresholds in humans are measured by "drop" or "sip" methods. The former reveals regional variations of sensitivity (e.g., hemiageusia) and hence is clinically preferable

(7). But variable spread of the drop complicates studies of normal human subjects (8).

Lewis (9) describes the derivation of psychometric scales of taste. Carrying this procedure further, Beebe-Center & Waddell (10) developed heteroqualitative scales using the subjective strength of a 1.0 per cent solution of sucrose, termed a "gust," as the unit. Gust-concentration curves are presented for quinine, sodium chloride, tartaric acid, and sucrose. Cameron (8, 11, 12) confirms earlier findings that isosweet curves of some sugars (glucose, galactose, lactose, glycerol, etc.) compared with sucrose are not linear but exponential. On the other hand, when these sugars are compared with one another, the isosweet curves are linear. Lichtenstein (13), apparently unaware of Cameron's work, also reports that the relative sweetness of glucose compared to sucrose varies with concentration. Dermer (14) has published a table showing the relative taste indices for acid, salty, sweet, and bitter substances.

Kloehn & Brogden (15) found a significant difference in thresholds for sodium hydroxide on the tip (average 0.24 *N*) and on the bud-free middorsum (average 0.290 *N*) of the tongue. Moreover, the subjects reported qualitative differences in response to stimulation of the two loci. This suggests that alkaline taste is not wholly a function of receptors of "common chemical sense" as proposed by Moncrieff (5, p. 111), but has a true taste component mingled with pain, common chemical sense, or both.

Interest in "taste blindness" to the thiourea compounds continues and has led to the discovery of an effective rodenticide,  $\alpha$ -naphthyl thiourea (16). Insensitivity to the bitter taste of phenyl-thiocarbamide (PTC) is relative, and even nontasters can taste PTC at high concentrations. Falconer (17) found a minimum frequency of thresholds at a concentration of 0.05 per cent and used sensitivity to this concentration as a criterion to separate tasters and nontasters. Of 629 subjects, 25.9 per cent of the men and 22.2 per cent of the women were nontasters. Women had significantly lower thresholds than men, and there was a small positive correlation between sensitivity to quinine and to PTC. Thresholds of smokers and nonsmokers did not differ significantly. According to Hall & Blakeslee (18) the immediate effect of smoking on thresholds varies; 73 per cent of the subjects experienced an increase, 20 per cent a decrease, and 7 per cent no change. Terry & Segall (19) report a significantly greater incidence of PTC

"taste blindness" in diabetic (41.2 per cent) than in nondiabetic (25.9 per cent) subjects.

The preference technique provides a method of determining taste thresholds in animals (4, 20, 21). Richter (4) found that adrenalectomy lowers the preference threshold for sodium chloride in rats and concluded that adrenal insufficiency alters the receptors. Hartridge (22), noting that taste buds respond to substances in the blood (e.g., decholin) as well as in the mouth, suggests "that the taste buds average the concentrations of substances in the blood and in the mouth. When a substance is deficient in the blood then its amount in the mouth must be increased in order that the concentration in the taste buds shall remain constant." Bare (23) also observed that adrenalectomy lowers the preference threshold for salt, but denies that it alters the receptive mechanism. Concentrations of sodium chloride required to evoke action potentials in the chorda tympani were not significantly different in normal (average 0.008 per cent) and adrenalectomized rats (average 0.010 per cent). Patton & Ruch (24) have pointed out that preference thresholds differ from absolute taste thresholds. The fact that normal rats do not prefer very weak salt solutions to water may only mean that motivation to discriminate is insufficient. The salt depletion provoked by adrenalectomy, however, may provide sufficient motivation for finer discrimination, just as hunger drives an animal to finer discrimination when food is the reward.

*Tongue, taste buds, and peripheral nerve pathways.*—Fish, Malone & Richter (25) enumerate the papillae of the rat's tongue. Fungiform papillae, each bearing a single apical taste bud, are confined to the rostral half of the tongue and average in number 180. The foliate papillae, averaging 12 in number, are grooves on the basolateral surface of the tongue; the walls of the grooves contain many taste buds. The single circumvallate papilla in the midline near the base bears numerous buds in the walls of the surrounding trench. Filiform papillae are spine-like processes free of taste buds. Elliott (26) found no taste buds in the newborn opossum; a 16 day old specimen had a single developing bud. The number increases slowly for about 115 days, then decreases, perhaps due to wear and tear of surface epithelium associated with weaning and shift to a coarse diet. Most of the buds are in the middle half of the tongue; the rostral-dorsal portion which contacts the nipple in suckling is sparsely populated.

Foley (27) enumerates the afferent fibers of the chorda tympani

in cat and dog. In cat the average count was 1,157 axons. Eighteen per cent were unmyelinated and were less than  $1.5 \mu$  in diameter. Myelinated fibers ranged from  $1.5$  to  $6.0 \mu$ . In dog, 2,205 fibers were counted; 23 per cent lacked myelin sheaths. The estimated ratio of afferent axons to taste buds in the anterior two-thirds of the tongue was 2:1 in cat and 3:1 in dog.

Pfaffman & Bare (28) present the perplexing report that rats continue to distinguish between sodium chloride solutions and water after section of the lingual (including the chorda tympani) and glossopharyngeal nerves. Acceptance thresholds were elevated in operated rats, but maximal preference for a solution of 0.9 per cent was the same as in normal rats. Histological studies revealed complete degeneration of lingual taste buds [Pfaffman (91)]. Patton & Richter (92) also failed to produce complete ageusia for quinine solutions by sectioning the lingual and glossopharyngeal nerves in rats; the rejection threshold was elevated but strong solutions were rejected. Two explanations are possible: (a) perception of bitter and salty solutions in supramaximal concentrations involves nongustatory end organs, or (b) the vagally-innervated laryngeal taste buds are sufficient for discrimination at high intensities.

The mechanism of taste bud excitation remains obscure. Frings (29) determined thresholds for various electrolytes in invertebrates, rabbits, and man and found that cations fall into a series according to stimulative effectiveness (reciprocal of thresholds). The series is the same as that of ionic mobility and of certain surface effects of the ions involved. He suggests that stimulation involves either penetration or some form of surface activity. Unfortunately for this theory, the anions fall into a series of stimulative effectiveness which is unrelated to any known physical or chemical properties of the members.

Frings (29, 30) questions the primacy of the gustatory submodalities, salty, sour, bitter, and sweet, suggesting that these may merely be familiar points in a continuous taste spectrum based on the stimulative powers of electrolytes and possibly nonelectrolytes. This theory under-rates the possibility of specific receptors and, if true, would make taste different from all other senses because recognition of quality would depend on numbers, not on the identity, of end organs stimulated. True, a simple theory of specific end organs will not suffice; Mueller's law of specific nerve energies does not invariably apply to submodalities. In cat Pfaffman (1)

isolated specific end organs only for acid; other end organs responded to both acid and bitter, or to both acid and salty. Responses to sweet are equivocal in cat (1, 31). Thus excitation of all receptors might be recognized as acid, of acid-bitter receptors as bitter, and of acid-salt receptors as salty. Subquality depends not merely on all-or-none excitation of particular fibers but on the pattern of excitation, and on the presence or absence of discharge in other fibers. Adrian (32) points out that the regional variation of lingual sensitivity to the different subqualities suggests a topographical organization of the cortical taste receptive area.<sup>1</sup> This would provide a neuronal substratum for different spatial patterns of excitation, corresponding to qualitative differences in stimulus.

*Central neural pathways for taste.*—The location of the secondary neurons of the taste pathways is undetermined. Allen's Marchi studies (33) clearly indicate that the afferent axons of the VIIth, IXth, and Xth nerves enter the tractus solitarius and terminate on the cells of its adjacent nucleus. Some authors, however, cling to the comparative neuroanatomists' contention that taste fibers terminate in the nucleus intercalatus of Staderini; indeed, one current textbook of neuroanatomy entirely eschews the term "nucleus intercalatus," referring to this group of cells as the "gustatory nucleus" (34). The question is not likely to be resolved by direct experiment because the proximity of the tractus solitarius and nucleus intercalatus precludes differential destruction.

Fibers from the bulbar nucleus reach the thalamus in close association with those of the ventral quintothalamic tract and the medial lemniscus. After lesions in the region of the tractus solitarius, degenerating fibers were traced through the dorsal part of the medial lemniscus to the posteroventral thalamus in guinea pig (35) and rabbit (36). The degenerated fibers were medial to the ventral quintothalamic tract (36). Conversely, lesions of the medial lemniscus in the midbrain result in retrograde degeneration in the rostral portion of the nucleus of the tractus solitarius (35). In rat, Patton & Ruch (24) found an elevated threshold for quinine following a lesion involving the dorsal portion of the medial lemniscus.

The thalamic relay nucleus for taste appears to be the nucleus

<sup>1</sup> Such a topographical organization was found by Gorschkow [*Mtschr. Psychiat Neurol.*, 10, 469 (1901) and *Neurol. Zbl.*, 20, 1092-93 (1901)] in the dog, although there are no modern studies to confirm it. The cortical area for taste was found in the anterior sylvian, ectosylvian, and compositus gyri, and the order of submodalities within this area was from anterior to posterior: bitter, sour, salty, sweet.

ventralis posteromedialis (arcuate nucleus), probably its most medial part. Lesions of this nucleus in monkeys raise the threshold for quinine as determined by the preference method (37, 38). Adler (39) reported a case of hemiageusia associated with a tumor encroaching on the medial tip of the arcuate nucleus. In cat (40) and monkey (41) an isolated area in the medial tip of the arcuate nucleus does not show evoked potentials on tactile stimulation of the body surface. Mountcastle & Henneman suggest that this may be the part of the nucleus which receives terminations of ascending fibers subserving taste. In monkeys, taste-sparing lesions of the inferior Rolandic cortex (see below) produce severe degeneration throughout the arcuate nucleus, save for its dorsomedial tip [Patton & Ruch (93)]. Gerebtzoff's degeneration studies (36) also indicate that taste fibers terminate medial to the trigeminal representation in the arcuate nucleus.

Location of the cortical receptive area for taste impulses remains unsettled. Börnstein (42) found gustatory defects in monkeys following ablation of the frontal and parietal operculum. Penfield & Boldrey (43) elicited taste sensations in only five of 163 patients submitted to cortical stimulation: the responsive foci were in the opercular region, precentral in one case and postcentral in the others. Guided by these reports and the finding that taste impulses relay in the arcuate nucleus, Patton, Ruch & Fulton (44) determined preference thresholds for quinine in monkeys and chimpanzees before and after ablation of the inferior Rolandic cortex to which the arcuate nucleus projects. Bilateral lesions confined to the free surface of the cortex, although destroying the entire face motor and sensory areas as well as portions of areas 5 and 7, produced no gustatory impairment. Deeper lesions, destroying varying amounts of the cortex overlying the insula, often produced severe but transient deficits. Recalling that Gerhardt (45) described sensory-type granular cortex (area 68 II gr) in the buried precentral operculum<sup>2</sup> of the chimpanzee, Ruch & Patton (47) opened the sylvian fissure with minimal damage to the free opercular surface and ablated both pre- and postcentral parainsular cortex. Such lesions produced taste deficits as severe as those resulting from larger lesions involving both parainsular and exposed inferior Rolandic cortex. The available evidence thus suggests a cortical localization of taste in the buried parainsular region. This

<sup>2</sup> Von Bonin and Bailey (46) confirmed this finding in the chimpanzee, but, in the macaque, were unable to detect granular cortex in this region.

may explain the rarity of gustatory responses to cortical stimulation in humans. Since the parainsular cortex may be considered an inferior extension of the sensory cortex, such a localization agrees with known topographical principles of thalamocortical projection. Taste would thus be localized inferior to the facial somatosensory representation in the cortex, corresponding to its extreme medial localization in the thalamus.

However, the parainsular localization cannot be accepted dogmatically because other investigators have adduced evidence implicating the insula itself. This theory is marred by the lack of any known thalamo-insular projection in primates (48). Gerebtzoff (49) thinks that Bremer's "masticatory" area in the rabbit is the cytoarchitectural homologue of the insula in higher mammals. Extirpation of Bremer's area abolishes taste sensation (50) and causes retrograde degeneration in a posteroventral thalamic nucleus which Gerebtzoff believes is a homologue of the primate arcuate nucleus (49). Moreover, gustatory stimuli alter the spontaneous electrical activity of the masticatory area (49, 51). Adler (52) also supported an insular representation of taste, citing a case of hemi-anesthesia contralateral to a temporal lobe tumor extending into the region of the insula. Epileptic seizures with gustatory aura have been associated with a tumor of the insula (53) and with a parietal opercular tumor (54). As Woolsey (55) notes, the experiments of Ruch & Patton are not conclusive because the effective lesions were close to the insula and, if thalamo-insular fibers exist in monkey, could have interrupted them. In any case, the results vindicate Börnstein's rejection (7, 56) of the classical hippocampal representation of taste and confirm his contention that taste and facial somatic sensation are related. Patton & Ruch (24) summarize the similarities between the two systems.<sup>3</sup>

<sup>3</sup> Since submission of this manuscript, the cortical projection zone of the chorda tympani has been determined in cats (94). A single shock to the chorda-lingual trunk, after section of the lingual component, evokes a surface positive potential in the cortex rostral to the face somatosensory area of Woolsey (95). The responses have a latency of 10-12 msec., and are abolished by destruction of the chorda tympani in the middle ear. Both cortices receive projections from one chorda tympani. The responsive zone, a few millimeters in area, is in the most rostral portion of the ectosylvian gyrus towards the orbital surface. No other cortical area explored, including the insular region, responds. Interpretation is somewhat obscured by the known presence in the chorda tympani of fibers mediating touch, as well as those conveying taste sensations (1), but the results suggest a close association between facial somatosensory and gustatory cortical connections. Similar experiments on monkeys are in progress.

## SMELL

*Thresholds and excitatory mechanisms.*—Descriptions of olfactometers abound (57, 58, 59); most are modifications of Elsberg's well-known blast injection apparatus (60). Foster & Dallenbach (61) briefly describe a large glass chamber with odor inlets, and humidity, pressure, and temperature controls. The subject bathes, dons an odorless envelope, and enters the chamber for tests. Wenzel (62), recalling that identification of odors in blast injection studies depends largely on stimulus pressure (63, 64), designed an apparatus to keep pressure constant throughout the blast. Curves of olfactory discrimination for phenyl ethyl alcohol were determined for four subjects by a modified method of single stimuli; the Weber fraction was about 0.15. A flaw in the method is the dependence of stimulus strength on pressure; control tests on one subject using odorless air yielded a pressure judgement curve not significantly different from the odor judgement curve. Le Magnen (65) deprecates the blast injection technique as an unnatural form of stimulation. He attempts to achieve constant flow by asking the subject to inhale evenly enough to maintain a constant pitch on a whistle in the air inlet. As Wenzel (57) observes, control of flow is thus made dependent on the subject's pitch discrimination. Le Magnen used this device to determine qualitative similarities between different odors by a method of cosaturation. The elevations of threshold for an odor after 10 min. of adaptation to the same odor and after 10 min. adaptation to a second odor were compared, and served as an index of the similarity between the two odors.

Hsü (66) investigated olfactory preferences for 21 odorous substances by the technique of factor analysis. Three of six factors extracted were clear-cut; one revealed the chemical property of unsaturation and the physiological quality of possible trigeminal stimulation, and the other two were chemically characterized by the presence of oxygen and nitrogen, respectively. Goetzel *et al.* (67 to 70) believe olfactory thresholds are indices of appetite and satiety. In normal subjects acuity decreases after a satisfying, freely-selected meal, but not after nonsatiating procedures—tasting sugar, ingestion of sugar in gelatin capsules, or intravenous glucose injections. Amphetamine dosage or intercibal feeding reduced appetite and freely-selected caloric intake at meal time (30 to 40 per cent of normal) and curtailed intercibal threshold decreases. The authors believe satiety requires both taste and ingestion of food [see Jano-

witz, Hanson & Grossman (71)] and is reliably reflected by decreased olfactory acuity. The reported average threshold changes are small and are not statistically treated. The mechanism relating olfaction to satiety and appetite is not clear to the reviewer.

The numerous theories of the olfactory excitatory mechanism are discussed in Moncrieff's monograph (5). The latest theory to attract attention, proposed by Beck & Miles (72, 73), is based on observations dating back to Faraday and Tyndall that odorous substances strongly absorb infrared radiation. The theory is that olfactory receptors radiate selectively, in accordance with their size and shape, wave lengths from 8 to 14  $\mu$ . The transient change in thermal equilibrium, resulting from exhibition of an odorous substance having absorption bands in this region, is postulated as the primary event in end-organ excitation. The experiments described suggest that insects can detect odorous substances enclosed in air-tight chambers equipped with infrared passing windows. Since these experiments have been reported only in abstracts, final evaluation must be postponed.<sup>4</sup> It is hoped that full treatment will clarify the mechanism of selective radiation and discuss the relation of odor to temperature of the stimulus. If the stimulus is at a higher temperature than the body, radiation to and not from the receptor should prevail. According to Young, Pletcher & Wright (74), the deuterioxy counterpart of *n*-butyl alcohol has the same odor as the natural nonisotopic alcohol, although the two substances have different infrared spectra. Conversely, *d*- and *l*-forms of some optical isomers are said to have different odors but identical infrared spectra (with the exception, of course, of polarized radiation).

*End organs.*—Unexplored for two decades, the histological structure of the olfactory mucosa has been carefully restudied by Clark & Warwick (75). In rabbit the receptors number 150,000 per sq. mm. and consist of a cell body, a fine proximal process (olfactory nerve fiber), and a coarser distal process. The last, the olfactory rod, is 20 to 40  $\mu$  long and 0.6 to 1.5  $\mu$  in diameter. Protargol stains reveal an internal structure of neurofibrillae often arranged peripherally, giving the rod a hollow appearance. Distally, the rod thins to 0.3 to 0.6  $\mu$  before terminating in a cup-shaped structure.

<sup>4</sup> Since submission of this manuscript, some of these studies have been published in more detail (96). The data reported support, but do not prove, the hypothesis advanced.

From the edges of the cup, olfactory hairs project in stellate formations and terminate in sharp points, minute vesicles, or darkly-staining, irregular bulbs. Viewed from the surface, these stellate formations vary in diameter (4 to 7  $\mu$ ), but are not zonally distributed according to size. Hairs of adjacent receptors do not overlap.

The fine, poorly-staining central fibers of adjacent receptors converge to form fascicles which traverse the cribiform plate. The resulting topographical projection is, however, disrupted at the surface of the bulb where the fibers form an intricate plexus before entering the glomeruli. Degeneration studies confirm the nontopographical organization of the projection of the mucosa onto the bulb. Ablation of the olfactory bulb produces detectable degeneration of receptors within a day and complete dissolution within a week. Partial ablations produce a depopulation of receptors over the entire mucosa with no evidence of local variation in intensity of reaction. Nor do such partial lesions produce selective atrophy of receptors of any particular size, as might be expected on the basis of the radiation theory. However, the lesions may have been too gross to show such organization. The nontopographical organization of the olfactory projection contrasts with the strict spatial organization of other sensory systems and is consistent with the lack of any known spatial or localizing element in olfactory perception.

The small size, short length, and inaccessibility of olfactory receptors preclude isolation of single primary units. However, employing microelectrode thrust into the deep layers of the olfactory bulb, Adrian (2, 3) recorded secondary neuron activity in fish, hedgehog, rabbit, and cat. A striking feature in mammals is the burst of impulses in the olfactory bulb accompanying each inspiration, even when the inhaled air is apparently odor-free. The receptors of fish are mechanically excitable by gentle stroking, and clear odorous fluids perfused through the sac evoke a less exuberant discharge than similar fluids containing particulate matter. The significance of mechanical excitability is not clear; it may increase excitability of central structures by providing a background of activity with which odor-evoked volleys may summate. Where such interaction might occur is obscure; electrical responses to nasal air currents are detectable as far centrally as the pyriform lobe. Mechanical excitability may account for the fact that stimu-

lus strength is related to stimulus pressure, not volume, in blast injection studies.

Addition of odorous substances to the inspired air increases the bursts, and often produces a continuous discharge, obscuring the rhythm imposed by respiration. The latter is particularly true of highly volatile substances (xylol, petrol, ether) which diffuse readily to all parts of the mucosa, including those which are relatively inaccessible to air currents. Adrian (32, 76) proposes that variation in pattern of excitation on the olfactory surface, depending on differences in diffusion of stimuli, is a possible factor in the discrimination of olfactory subqualities. A stumbling block for this theory is the lack of topographical organization whereby spatial patterns of excitation at the periphery might be projected onto the cortex in an orderly fashion. Occasional receptors appear to be specifically sensitive, but most respond indiscriminately to a wide variety of stimuli. However, adequate stimuli for receptors vary in different species. The rabbit's nose responds to fruity and aromatic smells (fresh grass, herbs, clove oil), but is insensitive to the stench of decaying animal matter. The cat, conversely, is insensitive to herbs or flowers, but responds strongly to decayed animal matter. Fish also respond to foul smells (a decoction of decayed alligator head was found most efficient!). The hedgehog has more versatile receptors, responsive to divers substances.

*Central pathways.*—Physiologists have long been confounded by the multiple central connections ascribed to the axons of the mitral cells. Standard textbooks describe three sites of termination: (a) the paraolfactory and septal areas, (b) the anterior perforated substance, and (c) the cortex of the uncus and hippocampal gyrus. These connections were deduced largely from examination of normal material and from Marchi studies of degenerating fibers. Recent investigations, employing more reliable methods, revise considerably the older concepts. Clark & Meyer (77) used Bielschowsky's silver stain and Glees' silver stain to trace degenerating fibers in the rabbit brain after ablating the olfactory bulb. Degenerating terminals were found in four sites:

(1) The superficial and plexiform layers of the prepyriform and periamygdaloid cortex. (2) Cortical-medial group of amygdaloid nuclei (including the central nucleus) and bed nucleus of the stria terminalis. Fibers reach the central nucleus and the bed nucleus of the stria terminalis via the anterior commissure, and appear to end in axodendritic synapses. The baso-lateral amygdaloid group was free of degenerating terminals. (3) The plexiform layer and, occasionally, around nerve

cells of the olfactory tubercle. Degeneration here was less massive than in the sites mentioned above. (4) The internal granular layer of the contralateral olfactory bulb (perhaps due to incidental damage to the anterior olfactory nucleus).

The septal areas, entorhinal cortex, and hippocampus were free of degenerating terminals. Using Marchi preparations, Allen (78) also failed to demonstrate degeneration in the hippocampus of dog after ablating the rostral half of the pyriform cortex, including the amygdaloid nuclei. The hippocampus thus appears to receive no direct fibers from the olfactory tracts; its afferent input is chiefly from the entorhinal cortex via the perforant and alvear tracts (78, 79, 80). Brodal (81) in reviewing the literature on the connections of the hippocampus concludes, "there is no reason to assume that the hippocampus is to any considerable extent concerned in receptory and associative functions" but rather is a "purely effector structure." He suggests that the hippocampus by its subcortical connections is "concerned in influencing subcortical reflexes, olfactory as well as others, as well as hypothalamic activity." Recalling earlier experiments in which olfactory stimuli or faradic stimulation of olfactory bulb, habenulae, anterior thalamic nuclei, pyriform lobe, or hippocampus evoked respiratory and cardiovascular reflexes, Allen (78) argues that Ammon's horn represents a mechanism for amplifying the simple olfactory reflexes.

Functional studies occasionally disagree with these anatomical findings; some conflicts are undoubtedly due to differences of terminology. In cats, Fox, McKinley & Magoun (82) stimulated the olfactory bulb, and recorded evoked potentials in prepyriform cortex, the anterior olfactory lobe, the olfactory peduncle, and the "pyriform lobe." The septum, diagonal band, amygdaloid nuclei, and hippocampus were silent. They did not explore the entorhinal cortex which is the main source of afferents to the hippocampus. However, they state that the potentials elicited from the caudal pyriform lobe diminished in amplitude as the recording electrodes approached the entorhinal area. Using the same technique and species, Rose & Woolsey (83) did observe spikes in the entorhinal area, but emphasized their smallness. Larger responses were recorded from the prepyriform and periamygdaloid areas, whereas the retrosplenial area, olfactory tubercle, hippocampus, and diagonal band were unresponsive. In dogs, Allen (84) elicited spikes in the rostral portion of the pyriform lobe by stimulating the bulb

and by nasal insufflation of odors. Hasama (85) obtained similar results in rabbits; the potentials were evoked by insufflation of odorous substances and were abolished by cocaineization of the nasal epithelium. In addition to the pyriform lobe, the mesial surface of the hemisphere was excitable; this has not been confirmed by other investigators. Adrian (3) noted conspicuous electrical alterations in the pyriform lobe of cats and hedgehogs following insufflation of odors, but did not report the exact positions of active foci. Penfield & Erickson (53, p. 56) failed to produce olfactory hallucinations in humans by stimulating the hippocampus, although stimulating the olfactory bulb elicited odors of "burnt leather."

Ablation studies are even less conclusive. In rats, olfactory discriminations are unaffected by lesions of the septum, amygdaloid complex, pyriform lobe, hippocampal complex, fornix, habenula, cortex around the central part of the corpus callosum (86, 87), or cortical projections of the anterior thalamic nuclei (88). Allen (89, 90) found that lesions of the pyriform-amygdaloid complex left intact simple olfactory conditioned reflexes but abolished more complex conditioned responses involving discrimination between cloves and asafetida. Neither type of response was altered by lesions destroying 90 to 100 per cent of the hippocampus.

#### LITERATURE CITED

1. PFAFFMAN, C., *J. Cellular Comp. Physiol.*, **17**, 243-58 (1941)
2. ADRIAN, E. D., AND LUDWIG, C., *J. Physiol. (London)*, **94**, 441-60 (1938)
3. ADRIAN, E. D., *J. Physiol. (London)*, **100**, 459-73 (1942)
4. RICHTER, C. P., *Harvey Lectures*, Ser. **38**, 63-103 (1943)
5. MONCRIEFF, R. W., *The Chemical Senses*, 424 pp. (John Wiley & Sons, New York, 1946)
6. DETHIER, V. G., AND CHADWICK, L. E., *Physiol. Revs.*, **28**, 220-54 (1948)
7. BÖRNSTEIN, W. S., *Yale J. Biol. and Med.*, **13**, 133-56 (1940)
8. CAMERON, A. T., "The Taste Sense and the Relative Sweetness of Sugars and Other Sweet Substances," 72 pp., in *Sugar Research Foundation (N. Y.) Sci. Rept. Ser. No. 9* (1947)
9. LEWIS, D. R., *J. Psychol.*, **26**, 437-46 (1948)
10. BEEBE-CENTER, J. G., AND WADDELL, D., *J. Psychol.*, **26**, 517-24 (1948)
11. CAMERON, A. T., *Can. J. Research [E]*, **22**, 45-62 (1944)
12. CAMERON, A. T., *Can. J. Research [E]*, **23**, 139-66 (1945)
13. LICHTENSTEIN, P. E., *J. Exptl. Psychol.*, **38**, 578-86 (1948)
14. DERMER, O. C., *Proc. Oklahoma Acad. Sci.*, **27**, 9-20 (1947)
15. KLOEHN, N. W., AND BROGDEN, W. J., *Am. J. Psychol.*, **61**, 90-93 (1948)

16. RICHTER, C. P., *Recent Progress Hormone Research*, **2**, 255-76 (1948)
17. FALCONER, D. S., *Ann. Eugenics*, **13**, 211-22 (1947)
18. HALL, A. R., AND BLAKESLEE, A. F., *Proc. Natl. Acad. Sci. U. S.*, **31**, 390-96 (1945)
19. TERRY, M. C., AND SEGALL, G., *J. Heredity*, **38**, 135-37 (1947)
20. SOULAIRAC, A., *Compt. rend. soc. biol.*, **141**, 745-47 (1947)
21. PATTON, H. D., AND RUCH, T. C., *J. Comp. Psychol.*, **37**, 35-49 (1944)
22. HARTRIDGE, H., *J. Physiol. (London)*, **103**, P34-P35 (1945)
23. BARE, J. K., Unpublished thesis quoted by Young, P. T., *Psychol. Bull.*, **45**, 289-320 (1948)
24. PATTON, H. D., AND RUCH, T. C., in *Howell's Textbook of Physiology*, 15th Ed., 370-84 (W. B. Saunders Co., Philadelphia, 1946)
25. FISH, H. S., MALONE, P. D., AND RICHTER, C. P., *Anat. Record*, **89**, 429-40 (1944)
26. ELLIOTT, R., *J. Comp. Neurol.*, **82**, 205-13 (1945)
27. FOLEY, J. O., *Proc. Soc. Exptl. Biol. Med.*, **60**, 262-67 (1945)
28. PFAFFMAN, C., AND BARE, J. K., *Am. Psychologist*, **3**, 284 (1948)
29. FRINGS, H., *J. Comp. Physiol. Psychol.*, **41**, 25-34 (1948),
30. FRINGS, H., *J. Exptl. Zool.*, **102**, 23-50 (1946)
31. ZOTTERMAN, Y., *Skand. Arch. Physiol.*, **72**, 73-77 (1935)
32. ADRIAN, E. D., *The Physical Background of Perception*, 95 pp. (Oxford Univ. Press, London and New York, 1946)
33. ALLEN, W. F., *J. Comp. Neurol.*, **35**, 171-204 (1923)
34. KRIEG, W. J. S., *Functional Neuroanatomy*, 553 pp. (Blakiston, Philadelphia, 1942)
35. ALLEN, W. F., *J. Comp. Neurol.*, **35**, 275-311 (1923)
36. GEREBTZOFF, M. A., *Cellule*, **48**, 91-146 (1939)
37. BLUM, M., RUCH, T. C., AND WALKER, A. E., *Yale J. Biol. Med.*, **16**, 175-91 (1943)
38. PATTON, H. D., AND RUCH, T. C., *J. Neurophysiol.*, **7**, 171-84 (1944)
39. ADLER, A., *Z. ges. Neurol. Psychiat.*, **149**, 208-20 (1934)
40. MOUNTCASTLE, V., AND HENNEMAN, E., *J. Neurophysiol.*, **12**, 85-100 (1949)
41. MOUNTCASTLE, V., AND HENNEMAN, E., *Federation Proc.*, **8**, 115 (1949)
42. BÖRNSTEIN, W. S., *Am. J. Physiol.*, **129**, P314 (1940),
43. PENFIELD, W., AND BOLDREY, E., *Brain*, **60**, 389-443 (1937),
44. PATTON, H. D., RUCH, T. C., AND FULTON, J. F., *Federation Proc.*, **5**, 79 (1946)
45. GERHARDT, E., *J. Psychol. u. Neurol.*, **48**, 329-86 (1938)
46. VON BONIN, G., AND BAILEY, P., *The Neocortex of Macaca mulatta*, 163 pp. (Illinois Monographs in Med. Sci., **5**, (4), Univ. Illinois Press, Urbana, 1947)
47. RUCH, T. C., AND PATTON, H. D., *Federation Proc.*, **5**, 89-90 (1946)
48. CLARK, W. E. LE G., AND RUSSELL, W. R., *J. Anat.*, **73**, 255-62 (1939)
49. GEREBTZOFF, M. A., *Arch. intern. physiol.*, **51**, 199-210 (1941)
50. BREMER, F., *Comp. rend. soc. biol.*, **89**, 432-33 (1923)
51. ECTORS, L., *Arch. intern. physiol.*, **43**, 267-98 (1936)
52. ADLER, A., *Z. ges. Neurol. Psychiat.*, **152**, 25-33 (1935)
53. PENFIELD, W., AND ERICKSON, T. C., *Epilepsy and Cerebral Localization*, 623 pp. (Charles C Thomas, Springfield, Ill., 1941)

54. SHENKIN, H. A., AND LEWEY, F. H., *J. Nervous Mental Diseases*, **100**, 352-54 (1944)
55. WOOLSEY, C. N., *Ann. Rev. Physiol.*, **9**, 525-52 (1947)
56. BÖRNSTEIN, W. S., *Yale J. Biol. and Med.*, **12**, 719-36 (1940)
57. WENZEL, B. M., *Psychol. Bull.*, **45**, 231-47 (1948)
58. RENNES, P., *Année psychol.*, **41**, 243-47 (1945),
59. FOSTER, D., SMITH, L. A., AND SCOFIELD, E. H., *Am. J. Psychol.*, **60**, 272-75 (1947)
60. ELSBERG, C. A., *Olfactory tests*, in *Medical Physics*, 821-24 (Year Book Publishers, Chicago, 1944)
61. FOSTER, D., AND DALLENBACH, K. M., *Am. Psychologist*, **3**, 253-54 (1948)
62. WENZEL, B. M., *J. Exptl. Psychol.*, **39**, 129-43 (1949)
63. ELSBERG, C. A., BREWER, E. D., AND LEVY, I., *Bull. Neurol. Inst. N. Y.*, **4**, 264-69 (1935)
64. JEROME, E. A., *Arch. Psychol.*, **39**, (274), 44 pp. (1942)
65. LE MAGNEN, J., *Année psychol.*, **43**, 249-64 (1947)
66. HSÜ, E. H., *Psychometrika*, **11**, 31-42 (1946),
67. GOETZL, F. R., AND STONE, F., *Gastroenterology*, **9**, 444-53 (1947)
68. GOETZL, F. R., AND STONE, F., *Gastroenterology*, **10**, 708-13 (1948)
69. GOETZL, F. R., GOLDSCHMIDT, M., WHEELER, P., AND STONE, F., *Gastroenterology*, **12**, 252-57 (1949)
70. GOLDSCHMIDT, M., RAIMONDI, P. J., AND GOETZL, F. R., *Am. J. Physiol.*, **155**, 439 (1948)
71. JANOWITZ, H. D., HANSON, M. E., AND GROSSMAN, M. I., *Am. J. Physiol.*, **156**, 87-91 (1949)
72. BECK, L. H., AND MILES, W. R., *Science*, **106**, 511 (1947)
73. MILES, W. R., AND BECK, L. H., *Science*, **106**, 512 (1947)
74. YOUNG, C. W., PLETCHER, D. E., AND WRIGHT, N., *Science*, **108**, 411-12 (1948)
75. CLARK, W. E. LE G., AND WARWICK, R. T. T., *J. Neurol. Neurosurg. Psychiat.*, **9**, 101-11 (1946)
76. ADRIAN, E. D., *Advancement of Sci.*, **4**, 287-92 (1948),
77. CLARK, W. E. LE G., AND MEYER, M., *Brain*, **70**, 304-28 (1947)
78. ALLEN, W. F., *J. Comp. Neurol.*, **88**, 425-38 (1948)
79. LORENTE DE NÓ, R., *J. Psychol. u. Neurol.*, **45**, 381-438 (1933)
80. LORENTE DE NÓ, R., *J. Psychol. u. Neurol.*, **46**, 113-77 (1934)
81. BRODAL, A., *Brain*, **70**, 179-222 (1947)
82. FOX, C. A., MCKINLEY, W. A., AND MAGOUN, H. W., *J. Neurophysiol.*, **7**, 1-16 (1944)
83. ROSE, J. E., AND WOOLSEY, C. N., *Federation Proc.*, **2**, 42 (1943),
84. ALLEN, W. F., *Am. J. Physiol.*, **139**, 553-55 (1943)
85. HASAMA, B., *Arch. ges. Physiol. (Pflügers)*, **234**, 748-55 (1934)
86. SWANN, H. G., *J. Comp. Neurol.*, **59**, 175-201 (1934)
87. SWANN, H. G., *Am. J. Physiol.*, **111**, 257-62 (1935)
88. LASHLEY, K. S., AND SPERRY, R. W., *Am. J. Physiol.*, **139**, 446-50 (1943)
89. ALLEN, W. F., *Am. J. Physiol.*, **128**, 754-71 (1940)
90. ALLEN, W. F., *Am. J. Physiol.*, **132**, 81-92 (1941)
91. PFAFFMAN, C. (Personal communication)

92. PATTON, H. D., AND RICHTER, C. P. (Unpublished data)
93. PATTON, H. D., AND RUCH, T. C. (Unpublished data)
94. PATTON, H. D., AMASSIAN, V. E., AND RUCH, T. C. (Unpublished data)
95. WOOLSEY, C. N., AND FAIRMAN, D., *Surgery*, **19**, 684-702 (1946)
96. MILES, W. R., AND BECK, L. H., *Proc. Natl. Acad. Sci. U. S.*, **35**, 292-310 (1949)

## PHYSIOLOGY OF VISION

BY RAGNAR GRANIT

*The Nobel Institute for Neurophysiology, Karolinska Institutet,  
Stockholm, Sweden*

Few fields in physiology are reviewed as regularly, fully, and adequately as vision. There have been two extensive and excellent reviews in this publication (1, 2). Several of the leading ophthalmological journals in England, France, Germany, and the United States have sections devoted to abstracting, the Swiss journal *Ophthalmologica* (Basel), in particular, having specialized on continuous reports of current literature and the new British reviewing journal, *Ophthalmic Literature*, providing good up-to-date reviews as well as abstracts. A book by Davson (3) gives an unbiased and neatly balanced account of the eye as a research field. The organization of the vertebrate retinal elements has been dealt with rather fully, in the light of recent evidence, in a summary by myself (4). Colour vision from the point of view of colour psychophysics and the measurement of colour is the subject of a book by the late Bouma (5), and information about the German work on dark adaptation during the war is an interesting feature of a book by Hamburger (6). The first volume of the revived *Documenta Ophthalmologica* has appeared, badly distorted by typographical errors, but containing several instructive summaries, among them a theoretical paper by Tschermak-Seysenegg (7) and accounts of the clinical developments of flicker analysis (8) and of electroretinography (9, 10). The next volume has just appeared and contains a belated account of the Colour Vision Conference in Cambridge 1947. Pirenne (11) has published a semipopular book on vision, particularly dealing with the so-called quantum fluctuation, which also is a central theme in a thesis by Bouman (12). It is actually so easy nowadays to obtain whatever information is wanted from current abstracting journals and summaries that it would seem to be of greater interest for the reader if this review were restricted to a presentation of a number of problems to which the author really can add the emphasis of continued interest or personal experience.

## PHOTOCHEMISTRY

Thanks to the now well-known work of Morton and his colleagues at Liverpool who demonstrated that Wald's retinenes 1 and 2 are the aldehydes of the corresponding vitamins A, the chemistry of light perception suddenly switched over from analysis of general colorimetric reactions to work with chemically known substances. This brought in the whole gamut of questions relating color absorption to molecular structure, effects such as the shift of absorption towards long wave-lengths in consequence of an increasing number of double bonds, application of the knowledge that such compounds exist in the form of resonance hybrids which in reality are alternative structural arrangements with somewhat different absorption spectra, understanding of the significance of free electrons, of dipole moments of solvents, etc., in short, the whole fascinating modern development of spectroscopic tools in the analysis of chemical structure and photochemical reactions.

The position now in this field is that the chemists and photochemists are faced with the task of studying the enzymatic and other reactions engaged in the breakdown and formation of photochemically important photopigments and that they have to produce from known ingredients existing in the retina substances that are likely to serve as substrates for modulators and dominators in the various systems known. Electrophysiologists, on the other hand, should supply the information wanted from various animals on the spectral sensitivities and adaptabilities of their eyes for comparison with the photochemical data. In the last year such information has only been obtained from the cat (13, 14, 52, 53) and the fly (15). To the photochemical work important contributions have appeared from research centres headed by Bliss, Morton and Wald, as well as from the new Vision Research Unit at the Institute of Ophthalmology in London.

The work of the Liverpool group is so far largely unpublished and only a fraction of it is available in brief reports and notes. Thus they have oxidized retinene from vitamin A (16) and have shown that synthetic retinene can be converted into vitamin A by an enzymatic reaction involving a reductase from rat liver and intestinal mucosa (17). Bliss (18) reports that a powdered acetone liver extract, containing alcohol dehydrogenase, reversibly oxidizes vitamin A to retinene. This substance is unspecific and attacks several aldehydes besides retinene. Wald, on the other hand, has

described an irreversible reduction of retinene by a system consisting of what he apparently holds to be a quite specific retinene reductase and an apoenzyme. The reductase contains the anti-pellagra factor nicotinamide as a central component. Vitamin E phosphate protects the vitamin A formed from oxidative destruction. He has published a summary of this work (19).

Ball, Morton *et al.* (20) have performed interesting experiments combining their synthetic retinene with various proteins and amino acids and thus, in some cases, obtained colored photoproducts with maxima from 5,000 to 5,250 Å. A photosensitive substances with maximum in 5,350 Å was produced with *p*-aminobenzoic acid.

TABLE I  
WAVE-LENGTHS OF MAXIMUM ABSORPTION IN Å

Rhodopsin	5,000				
Iodopsin				5,600	
Dominators		5,000		5,600	
Modulators	4,500-4,650	5,000	5,200-5,300		5,800-6,100
Vitamin A in conc.					
H <sub>2</sub> SO <sub>4</sub>	4,650		5,300	5,900	6,200*
Vitamin A in conc.					
H <sub>3</sub> PO <sub>4</sub>	4,400-4,800		5,200		6,000
Retinene, in conc.					
H <sub>2</sub> SO <sub>4</sub>	4,400-4,600		5,200	5,600	6,640*
Retinene, in conc.					
H <sub>3</sub> PO <sub>4</sub>	4,700	5,000		5,500	5,900

\* Shown better with the antimony trichloride reagent.

From this result they also concluded that Lythgoe's indicator yellow, formed in the course of breakdown of visual purple, was a fortuitous artefact due to the combination of retinene with retinal proteins. But objections against this view have been raised by Dartnall (21) and indirectly by Bliss (22) (cf. below). The great possibilities of retinal photochemistry are clearly demonstrated by Table I from their paper.

The table shows the maxima of a number of narrow photosensitive bands obtained from retinene and vitamin A by the procedures listed. These synthetic 'modulator analogues' were also thermolabile. They faded at different rates suggesting several specific products rather than one product with several maxima. The authors fully realize that their procedures have been unphysiological, yet, by instituting a comparison with electrophysiologically obtained dominators and modulators, they wanted to show that the 'modulator analogues' represented potentialities that have to be explored.

In view of what has been said about photochemical possibilities one may legitimately ask with what degree of accuracy the scotopic dominator of the fully dark adapted vertebrate eye is represented by individual retinal elements. The on-elements and a number of on/off-elements, perhaps the majority, give a somewhat narrower visual purple curve; but several on/off-elements are provided with humps, even as far out as to be in the violet region of the spectrum (14), a variability that well may illustrate the plasticity of the conjugated proteins serving as retinal photopigments. Unfortunately there is very little likelihood that the chemists ever will succeed in extracting these substances from individual retinal elements. I have dealt fully with this question elsewhere (4).

By a chromatographic procedure Wald (23) too has obtained from vitamin A a highly photosensitive substance with maximum at 5,450 Å, reminiscent of the electrophysiologically determined sensitivity curve of the waterbeetle *Dytiscus marginalis* (24). This substance also yields, with sulfuric and hydrochloric acids, colored products which are markedly photosensitive. From the chicken retina he has isolated a new carotenoid, named galloxanthin, which he suggests, may serve as a differentiating filter (25).

The early phase of the breakdown of visual purple has occupied the attention of Bliss (22). He confirms the existence of Lythgoe's transient orange and indicator yellow. Bliss' results may be briefly summarized in the statement that the transient orange, formed photochemically in the first phase of bleaching by light, is transformed into acid indicator yellow by a thermal reaction. The latter substance is the precursor of retinene as well as of basic indicator yellow. The formation of retinene is nonenzymic from its precursor, the acid indicator yellow, which also may deliver vitamin A directly. We have already discussed the enzymic processes in the production of vitamin A from retinene.

Whilst the analysis of the chain of events in the breakdown of visual purple is of great importance for an understanding of the chemistry of the components taking part in it, it is questionable whether the process itself is of importance for the primary visual act. Both Bliss (26, 27) and Dartnall (21) raise this question. Elsewhere (24, p. 245) I have pointed out that considerable changes in sensitivity of the retina, as determined by electrophysiological methods, may occur after adaptations to colour which cannot have

bleached visual purple in the retina because they did not even succeed in bleaching visual purple in solution. Bliss has been led to it by his analysis of the squid photopigment, named cephalopsin, which he now (27, 28) has obtained in a state of relatively high purity liberated from disturbing melanin. Its absorption curve follows that of visual purple relatively closely. But the substance itself does not change under the influence of light. It is unbleachable. However, after treatment with formaldehyde, it changes into something resembling real visual purple, forming indicator yellow (27) and retinene (26). This suggests that it, after all, may serve as a visual pigment and that the bleaching process may be a secondary development, specific for vertebrates. Indeed, one could imagine several reasons for such a development in the course of evolution. Dartnall (21), on theoretical grounds, suggests that activation of a visual purple chromophore by a light quantum may be "succeeded by a chemical process resulting in an electron transfer down the conjugated chain to the protein base and thence, *in vivo*, to the retinal end organ to which, in all probability, the visual purple molecules are attached." This concept also makes the bleaching process an event of secondary importance and suggests a reinterpretation of our experiments comparing quantity of visual purple and retinal sensitivity (24).

Weale (29) has recalculated the molecular weight of visual purple from a formula proposed by Houstoun (102). The new value 45,600 would give two chromophores per carrier instead of only one as proposed in the computation of Broda, Goodeve & Lythgoe (30) [but cf. Collins & Morton (106)]. Dartnall (31) has quantitatively explored the possibilities of spectral shifts obtained by indicator yellow as a filter.

St. George points out that in the red portion of the spectrum beyond 6,500 Å, thermal energy must begin to supply part of the activation energy necessary for breaking down the visual purple molecule (32) because the temperature coefficient of bleaching continues to rise towards the extreme red. Corresponding results on man are reported by de Vries (33), according to whom the sensitivity to long wave-lengths increases when the observer is in a hot bath. These results explain Göthlin's old observation (34) that beyond 6,500 Å there is a shift of cone sensitivity relative to rod sensitivity in favour of the latter.

## EXCITATION AND INHIBITION IN THE RETINA

*General observations.*—Primitive eyes continue to supply important information even though some caution is necessary in applying the results to the vertebrate retina. Thus Hartline (35) has noted in *Limulus* that the single fibre discharge from one facette may be depressed to some degree by illumination of a nearby facette. This effect presupposes the intactness of the nervous plexus at the base of the visual cells. Parry (36) has studied the ocellus of a locust (*Migratoria migratoroides*). The ocellus is connected with its ganglion by a 1 mm. long nerve,  $25\mu$  in diameter, never conducting any impulses. However, when the ocellus is illuminated, the nerve, in contradistinction to that of *Limulus*, becomes polarized instead of depolarized. Upon cessation of illumination the electrical status of the nerve returns to normal with an overswing of depolarization. At this moment the corresponding electrotonic change in the nerve, spreading to the ganglion, sets up impulses which can be recorded from the circumoesophageal commissure. Thus, in this eye, the effect of light is ultimately translated into a positive instead of into a negative electrotonic response (to use less accurate but conventional terms), and the disappearance of positivity ending in a negative overswing produces an off-effect. Here then is a picture of an electrical mechanism for the off-effect very much along the lines suggested by the author (24) to account for the connection between the electrical component potential PIII and the off-effect in the vertebrate eye. There is even the overswing of the slow PIII potential in the opposite direction (that of PII) demonstrated long ago (37) in the frog's eye.

Is there anything else in the vertebrate retina suggesting correlations? One is reminded of the curious fact that, when isolated spikes are recorded from the mammalian eye by means of the microelectrode technique, the pure on- and off-elements respond to opposite directions of a polarizing current passed through the bulb, provided that the microelectrode is near the point of entrance of the galvanic current. The pure on-element discharges in response to the cathode, the pure off-element in response to the anode (38, 39). The on/off-elements, by far the most numerous and important ones in the vertebrate retina (40), are anodal or cathodal, in the sense that some of them respond with a lower threshold to the anode, others to the cathode, apparently depending upon whether in their design the anodal or the cathodal component is the

dominant one. In consequence of their 'ambipolar' design it is sometimes possible to rebalance them by light adaptation and, since, in the dark, they reassume their original polarity long before the threshold has returned to normal, it is clear that the polar properties are independent of photochemical sensitivity as such (41). One is reminded of Hartline's observation of two layers of cells in Pecten (42), the one responding to onset, the other to cessation of light. It would be interesting to have this simple eye tested by polarization. Are there, in the vertebrate eye, real 'anodal' and 'cathodal' cells or are the anodal cells of opposite orientation, say, stimulated by Polyak's so-called centrifugal bipolars (43)?

Each retinal element is a little nervous centre of its own for us to explore, a network of several cells joined to the ganglion cell forming the nerve fibre. Surveys are needed as well as minute analysis of individual centres. The polarity test has given some more information when combined with threshold measurements before and during polarization. The on-elements which appear to be pure visual purple rods (14) have the further property of not altering their light sensitivity very much under the influence of polarization (39). In off- and on/off-elements, however, large changes are often noted in the light thresholds during polarization, facilitations by the exciting pole and inhibitions by the opposite pole. These effects, particularly marked in anodal elements, are often restricted to either the on- or the off-component and thus polarization may be described as a method of altering the off/on-ratio measured by the respective threshold sensitivities. Evidently then, the lack of an effect of polarization upon the pure on-elements can only signify a lack of structures sensitive to polarization apart from suggesting that such structures cannot be localized to the straight forward path, receptor-bipolar-ganglion, common for all elements. The structures maintaining the off/on-ratio are to be found in the internuncial cells. This adds significance to the normal variation of the off/on-ratio at the threshold which covers a large range of more than 100,000 (40). Very complete statistical distribution curves have been plotted for the cat's retina by Germandt (44). It seems as if, in general, visual purple rods tended to make elements cathodal and give them a low off/on-ratio.

What is the significance of the off/on-ratio, regarded from the point of view of visual performance? In a general way one might

say that a variation in off/on-ratio adds individuality (or 'local sign') to each element, provided that the eye or the head moves so as to bring this mechanism of differentiation into play. Lord & Wright (45) have detected rapid flicks of 3 to 14 min. of arc recurring at a frequency of about 2 to 3 per sec., each flick lasting 0.02 to 0.03 sec. Such eye movements could form the basis of a scanning device for discrimination. Unless artificially fixed for the purpose of isolating eye movements, the head is, also, moving all the time. [Eye movements have continued to interest two teams in England (46-49).] The presence of on- and off-components in most elements, as well as of internuncial mechanisms capable of emphasizing either component by redistributing inhibition and excitation within them, makes it probable that one but rarely encounters functions in terms of impulse frequency that are proportional to primary photochemical events. Thus, for instance, Gernandt (50, 51) reports that the effect of light adaptation depends upon the off/on-ratio so that the drop in threshold tends to be proportionately greater in the more sensitive component. The off-component is, so to speak, the 'live' end of more off-sensitive element, the on-component of a more on-sensitive element. Very striking too in his work (50, 51) was the extreme variability of the on/off-elements with respect to the degree of adaptability, some adapting very much, some hardly at all, and a few even becoming more sensitive owing to a suppressed component at 'on' or at 'off' coming to the fore because of a change in the synaptic state of balance between excitation and inhibition maintaining the off/on-ratio.

*Selective effects of wave-length of stimulus.*—Donner (52, 53) has measured the impulse frequency-time curve at 'on' and 'off' in 100 elements of the cat's eye and showed that in elements with selective sensitivity to wave-length the response to red rises at a faster rate than the response to green and that a late maximum is especially characteristic for blue stimuli. In tracing these curves through the spectrum he found three maxima, one in 6,000 Å, one in 5,200 Å, and one in 4,600 Å, corresponding to the maxima of the three predilection areas for modulators in this eye (24). A characteristic feature of the early and fast 'red' response curve was a secondary rise in the blue. Modulators within the same three predilection areas reappeared in a study of colour reception by the polarization method (13, 54).

The peripheral mechanism of wave-length discrimination may be poor in the cat but it is definitely present, traceable behind a 'smoke screen' of visual purple-rod receptors. Thus, for instance, Gernandt (50) has noted negative correlation coefficients of 0.4 to 0.5 between threshold on- and off-sensitivities of the two contrasting colours red and green (72 elements), whereas no correlations whatever were found for the pairs red-blue and green-blue. In addition he has demonstrated a high degree of selective sensitivity to adaptation with the three colours. Recalling that the more sensitive component of an on/off-element is primarily attacked by the stimulus, we may conclude that after illumination with, e.g., red light the red on- and off-components of highly red-sensitive elements will be desensitized by selective adaptation, whilst the green on- and off-components in other elements are then ready to create 'green' by 'successive contrast' afterwards.

This being so one would expect the off/on-ratio as such to give some clue to color sensitivity. Actually there are elements in which the off/on-ratio increases considerably towards the two ends of the spectrum (50). Such elements were studied at supra-threshold levels of intensity by myself (55), all wave-lengths being adjusted to the energy required for equal visual purple activation. These experiments were a first attempt at mixing colours in terms of an objective index, such as impulse frequency per sec. for an isolated spike. Assuming a red of 6,400 Å and a green of 5,200 Å giving a response differing in off/on-ratio, higher for the red than for the green (a reasonably common type of element in the cat's eye), what happens when, in the dark adapted eye, the two colours are mixed at half energies in order to preserve constant activation of visual purple? Do the frequencies summate, does one obtain intermediate values or does either of the two impress its frequency distribution at 'on' and 'off' upon the sum? The experiments proved that in most elements of this type the red wholly dominated and impressed its value for the off/on-ratio upon the sum but there were also some cases in which green predominated. Therefore, when elements contain receptors with different but overlapping spectral sensitivity curves, either of the two curves may be suppressed in the region of overlap, a mechanism that must be of some importance for the concept of 'modulators' as well as for an understanding of the mechanisms involved in colour mixture and colour neutralization.

In the section on photochemistry some other experiments belonging to this section were mentioned because of their interest for the question of single elements as detectors of visual purple and a possible photochemical mechanism contributing to modulation.

#### ELECTRORETINOGRAPHY

One of the more important developments at the present time is the acceptance of the recording of the electrical response of the human eye, the ERG into standard clinical practice. Several of the leading eye hospitals in Europe are taking it up, generally by means of the technique of Karpe (56) which is well standardized on a large normal material and which, by employing the contact glass electrode, fairly successfully removes extra-retinal sources of error, as well as local variations due to the placement of the electrodes on the bulb. It can, in fact, without much ado, be applied to out-patients (9). Apart from the obvious use of electroretinography in cases where the ocular media show some opacity, clinical observations suggest that it is of prognostic value in certain types of disease and helps to determine whether surgical treatment should be undertaken or not (10, 56). All this accentuates the need for further studies of the human ERG.

Monnier (57) has reported his work in electroretinography, and there are several papers by Motokawa & Mita (58-63) which have become accessible after the war. Tansley has published a brief review of earlier work (64). In a study of dark adaptation Karpe & Tansley (65) have again brought forward more evidence to the effect that the b wave of the human ERG is chiefly determined by rods. By suitably arranging the experiment it can be made to reproduce the course of dark adaptation. A shift towards the long wave-lengths in the spectrum in modest light adaptation, noted by Motokawa & Mita (63), suggests that a minor fraction of the b-wave may be due to cones. In full light adaptation the b-wave is known to disappear. The diminution of the b-wave towards the periphery has been confirmed (57). Monnier (57) suggests the use of the ERG in perimetry by measuring the size of the b-wave but, in view of the spread of light in the bulb and the fact that large scotomata may occur without any diminution of the b-wave (56), it is doubtful whether perimetry could be developed on this basis. It would only seem possible by measuring the amount of energy necessary for a constant small response.

Karpe (56) showed, that when one eye was illuminated, a slow response looking like the c-wave occurred in the other eye even when the latter was blind. This observation has been confirmed by Monnier (57). The effect was explained as a consensual pupillary reflex. The very large c-waves, described by Motokawa & Mita (59), suggest a considerable extra-retinal component of this kind. In their work the electrode was on the bridge of the nose and thus must have picked up symmetrically from both eyes, unless the nonilluminated eye was well screened and heavily atropinized. This method of recording was suggested by their important observation (58) that in electroencephalography the intra- (and certainly also the extra-) retinal potentials are a serious source of error when the electrode is anywhere near the eye, something to remember in the now so popular recording of visual effects in electroencephalography. In electroretinography another great disadvantage of their technique is that the ERG is only one-tenth of its normal size and so has to be ten times more amplified. The curious double b-waves noted by the Japanese authors (59) have never been seen by anybody else and should be confirmed with contact glass electrodes before they can be accepted [they cannot be compared with humped b-waves in frogs (24)]. The second b-wave may be coming from the other eye, be the source then extra- or intra-retinal.

Both Monnier (57) and Motokawa & Mita (60, 62, 63) have studied the effects of wave-length and stimulus intensity on the b-wave, Motokawa (61), in addition, comparing the ERG with parallel measurements of brightness discrimination and visual acuity. In view of the overwhelming evidence for the association of the human b-wave with visual purple-rods, quantitative correlations with cone functions are difficult to interpret. Similarly it is difficult to interpret correlations with area illuminated (60) because of the effect of stray light within the bulb on the size of the b-wave used as index, as pointed out above.

Wulff (66) has tried to find out whether the frog's eye, as long as it is illuminated, maintains an ERG. This was found to be the case for illumination periods up to one hour. The ratio between retinal action potential and resting potential has been found to be approximately constant (67), an interesting contribution to an old problem. It deserves to be followed up properly.

## PSYCHOPHYSICS

Psychophysical methods, tests, and theoretical work were discussed very adequately by Chapanis (2) last year. There are also the reports to the Paris meeting of the International Commission on Illumination. The important Report No. 4 by le Grand (68) deals with nearly all the topics that have been in the foreground in psychophysical work during the last five years and contains a bibliography of 354 papers. I am adding some recent contributions to selected problems.

*Colour vision and luminosity.*—Hartridge (69, 70) has summarized the evidence for his polychromatic theory. Perhaps the most important aspect of his work is the resourceful criticism of the weak spots in the armour of the more dogmatic kind of trichromatism which, in the face of formidable histological and physiological evidence for the complexity of the retinal mechanisms, insists upon deriving all properties of colour vision merely from the shape of three absorption curves. We have seen above, for instance, what may happen when a red and a green stimulus overlap on a single on/off-element. And, in psychophysics, it seems that even fundamental phenomena, such as saturation and the luminosity function including the perception of white, can hardly be regarded as properly understood on the trichromatic theory. Hartridge (71) has repeated and confirmed Hering's experiment demonstrating that a match between monochromatic yellow and a mixture of red and green rays does not remain a match at all visual angles. He has also prepared filter combinations (72) which in different ways produce a yellow "as nearly as possible alike in hue, saturation and brightness." The adaptive effects given by these filters were very different. These arguments can hardly be disregarded.

The exploration of colour reception with small fields, in the hands of Thomson (73), continues to yield interesting results. Expanding his observation that the energy increment necessary to evoke a just noticeable difference of brightness is a function of wave-length, he has collected a large amount of data on this phenomenon at different brightness levels. Plotting the logarithms of intensity discrimination (defined in the customary way) as functions of wave-length at different equal brightness levels he finds minima corresponding to the modulator regions, provided that low brightness levels are measured. Their disappearance at higher brightness levels is interpreted on the basis of the idea that domi-

nators might become preponderant at such levels. This is by no means improbable since the dominator activity, so easily demonstrable in animals after good light adaptation, may well signify a recombination of several modulators which then appear coupled to the same final common path, say, of the type set up by diffuse ganglion cells collecting from several bipolars.

A trichromatic pattern (as pointed out above) is definitely woven into the texture of colour vision but is not the only pattern that can be traced in this fabric. The trichromatic curves obtained by various methods, psychophysical as well as electrophysiological ones, do not differ very much. They have been re-determined by de Vries (74) by a method previously used by Stiles (75) with whose results de Vries's curves are in good general agreement. Whether or not these curves mean receptor absorption is another matter.

De Vries (76) also has some interesting observations on luminosity determined by adjusting a (generally) red and a green field to minimum flicker fusion and measuring the ratio red:green under the influence of a number of variables. This is a convenient method of spotting changes in the luminosity function which was found to obey the summation law only for brightnesses below 50 photons. For higher intensities it was necessary to add more red. Coloured backgrounds were also tested and differences noted between normal trichromats and colour blind observers but individual variations were considerable. There were also significant effects of previous adaptation to coloured fields on his index, indicating that the component absorption curves contributing to the luminosity function were changed in a differential fashion by this factor (Schouten's  $\beta$ -adaptation). How very little these phenomena are understood is obvious from the fact that adaptation to green fields actually caused an increase of the sensitivity of green relative to red. (Cf. the parallel with Gernandt's work mentioned above.)

The possible role of inhibition in colour vision has been studied by Segal (77); Judd (78) reviews the evidence by which we have learned to know the colour perceptions of the partially colour blind ending up by developing Munsell notations for protanopes and deuteranopes. Chapanis (79) reports a critical analysis of pseudoisochromatic plates. A study of one totally colour blind is reported by a group headed by the late Hecht (80), who did so

much for visual research in the United States and gained an international reputation in this field. There is one interesting observation, new to psychophysics: the function log critical frequency-log stimulus intensity has a low and a high intensity branch of different slopes showing that in this visual purple-rod eye there must be rods of at least two different kinds, a conclusion that for some time has been maintained on different evidence in electrophysiological work (24). The absence of an effect of stimulus area upon the critical frequency is also an observation of great theoretical interest but it has previously been made by Ajo & Teräskeli (81). The agreement with the scotopic luminosity curve of normals—Hering's great discovery—was not as perfect as had been expected. The scotopic luminosity curve of the normal eye was obtained by Flamant & Stiles (82) in a study of the directional effect mainly devoted to establishing the absence of this effect on visual purple-rods by a new indirect method. Ivanoff's important observations (83) on curious fluctuations of visual acuity in scotopic vision might be mentioned in this connection.

*Threshold phenomena.*—The quantum measurements of Hecht, Schlaer & Pirenne (84) and van der Velden (85) are criticized by le Grand (68), who thinks the corrections applied by the former "à vrai dire incertains" and the calculations of the latter "un peu incertains." Flamant & Stiles (82) point out that there are biological variations also to be taken into account. This, of course, is true as all the work on the fluctuating "brain waves" shows. The Dutch group, in a recent publication (85), maintains that for stimulation of the rods two quanta have to fall within 0.04 sec. on an area of 12 minutes of visual angle. The same value is obtained for the cones for an area of 2 to 4 minutes of visual angle. Otero, Plaza & Salaverri (86), in a study of night myopia, which reduces visual acuity by some 50 per cent, want to reduce the quantum values accordingly.

Whatever factors enter into the fluctuation at the threshold a statistical approach is, of course, valuable, as is particularly evident from Baumgardt's work (87, 88) in which Ricco's and Piper's laws and the reciprocal relationship between time and intensity are derived from the assumption that a local potential within a brief time sets up an impulse, an interesting analysis doing away with the so-called secondary chemical reaction of "psychophoto-

chemistry." In basing his reasoning on the local potential of peripheral nerve instead of on the retinal action potential Baumgardt may perhaps be said to "bring coals to Newcastle."

Bouman's thesis (12) *On the quanta explanation of vision* is too extensive for review here. The two-quantum concept of Bouman & van der Velden (85) is confirmed. The methods are reported rather fully. The most important conclusion would seem to be that, if by choosing different wave-lengths, rod and cone responses are separated from one another, their effects summate at the threshold showing that rods and cones must be interconnected at some point in the path. It is not quite clear whether or not a double monochromator was used or if steps were taken to ensure corresponding selectivity by other means. Bouman also finds variations in colour sensitivity along the spectrum in her own and van der Velden's eye and suggests an explanation in terms of modulator activity. Thomson's earlier work (89) along somewhat similar lines should be consulted for a comparison of methods and results.

Auerswald (90), ten Doerschate (91), and Haig (92) also report a number of valuable studies of scotopic thresholds in relation to receptor patterns in the retina. Baker (93) has measured the course of foveal light adaptation and finds interesting fluctuations suggesting electrophysiological parallels.

*Stereoscopic effects, evaluation of distance, etc.*—It is impossible to do more than draw attention to important work carried out in this field at the psychological laboratory of Columbia University (94–100). The scope of this work, ranging from monocular movement parallax thresholds (94–97) over interposition, (98) stereoscopic acuity (99) to a comprehensive analysis of the Pulfrich phenomenon (100), would necessitate a review all by itself.

*Addendum.*—At the time of typing the final manuscript I received an important paper by Birukow (101) showing the absence of a Purkinje shift in tadpoles at a very early stage. The training tests were combined with an analysis of its retinal receptors. The cones proved to be further developed than the rods, a fact in agreement with the result of his optometric training test.

Because of their importance for the problems discussed, I would like to add briefly that Rushton (103) recently has studied the elements in the cat retina and found them to be derived from large single ganglion cells of the diffuse type, a fact in good agreement with all the physiological evidence for their complex receptor

patterns. Motokawa (104) has used the polarization technique in an interesting new fashion to determine colour sensitivity in man and frog, and his results reproduce the averaged modulator regions found in various animals by the micro-electrode technique. Finally, there is a study of rod structure with the electron microscope by Sjöstrand (105) which brings out new structural details in the outer limbs of these receptors.

## LITERATURE CITED

1. WEYMOUTH, F. W., *Ann. Rev. Physiol.*, **6**, 391-426 (1944)
2. CHAPANIS, A., *Ann. Rev. Physiol.*, **10**, 133-56 (1948)
3. DAVSON, H., *Physiology of the Eye*, 438 pp. (Blakiston Co., Philadelphia, 1948)
4. GRANIT, R., *Ergebn. d. Physiol.* (In press)
5. BOUMA, P. J., *Physical Aspects of Colour* (Philips Technical Library, Eindhoven, 1947)
6. HAMBURGER, F. A., *Das Sehen in der Dämmerung* (Springer, Wien, 1949)
7. TSCHERMAK-SEYSENEGG, A., *Doc. Ophthalm.*, **2**, 10-91 (1948)
8. WEEKERS, R., AND ROUSSEL, F., *Doc. Ophthalm.*, **2**, 130-92 (1948)
9. KARPE, G., *Doc. Ophthalm.*, **2**, 268-76 (1948)
10. KARPE, G., *Doc. Ophthalm.*, **2**, 277-96 (1948)
11. PIRENNE, M. H., *Vision and the Eye*, 187 pp. (Pilot Press, London, 1948)
12. BOUMAN, M. A., *On the Quanta Explanation of Vision* (Doctoral thesis, W. Junk, Utrecht, 1949)
13. GRANIT, R., *J. Neurophysiol.*, **11**, 253-60 (1948)
14. DONNER, K., AND GRANIT, R., *Acta Physiol. Scand.*, **17**, 161-69 (1949)
15. DONNER, K., AND KRISZAT, G., *Arkiv Zool. [A]* **42**(14), 1-7 (1949)
16. BALL, S., GOODWIN, T. W., AND MORTON, R. A., *Biochem. J.*, **40**, 59P (1946)
17. BALL, S., GLOVER, J., GOODWIN, T. W., AND MORTON, R. A., *Biochem. J.*, **41**, 29P (1947)
18. BLISS, A. F., *J. Biol. Chem.* (In press)
19. WALD, G., *Science*, **109**, 482-83 (1949)
20. BALL, S., COLLINS, F. D., MORTON, R. A., AND STUBBS, A. L., *Nature*, **161**, 424-26 (1948)
21. DARTNALL, H. J. A., *Nature*, **162**, 222 (1948)
22. BLISS, A. F., *J. Biol. Chem.*, **172**, 165-78 (1948)
23. WALD, G., *J. Gen. Physiol.*, **31**, 489-504 (1948)
24. GRANIT, R., *Sensory Mechanisms of the Retina*, 412 pp. (Oxford University Press, London, 1947)
25. WALD, G., *J. Gen. Physiol.*, **31**, 377-83 (1948)
26. BLISS, A. F., *J. Gen. Physiol.*, **26**, 361-67 (1943)
27. BLISS, A. F., *J. Biol. Chem.*, **176**, 563-69 (1948)
28. BLISS, A. F., *Biol. Bull.*, **95**, 242 (1948)
29. WEALE, R., *Nature*, **163**, 916 (1949)
30. BRODA, E. E., GOODEVE, C. F., AND LYTGOE, R. J., *J. Physiol. (London)*, **98**, 397-404 (1940)
31. DARTNALL, H. J. A., *Brit. J. Ophthalmol.*, **32**, 793-811 (1948)
32. ST. GEORGE, R. C. C., *Federation Proc.*, **8**, 137 (1949)
33. DE VRIES, H., *Experientia*, **4**, 357 (1948)
34. GÖTHLIN, G., *Kgl. Svenska Vetenskapsakad. Handl.*, **58**, No. 1, 89 (1917)

35. HARTLINE, H. K., *Federation Proc.*, **8**, 69 (1949)
36. PARRY, D. A., *J. Exptl. Biol.*, **24**, 211-19 (1947)
37. GRANIT, R., AND THERMAN, P. O., *J. Physiol. (London)*, **91**, 127-39 (1937)
38. GERNANDT, B., AND GRANIT, R., *J. Neurophysiol.*, **10**, 295-302 (1947)
39. GRANIT, R., *J. Neurophysiol.*, **11**, 239-52 (1948)
40. GRANIT, R., AND TANSLEY, K., *J. Physiol. (London)*, **107**, 54-66 (1948)
41. DONNER, K., AND GRANIT, R., *Acta Physiol. Scand.*, **18**, 113-20 (1949)
42. HARTLINE, H. K., *J. Cellular Physiol.*, **11**, 465-78 (1938)
43. POLYAK, S. L., *The Retina*, 607 pp. (Univ. Chicago Press, 1941)
44. GERNANDT, B., *Acta Physiol. Scand.*, **15**, 286-89 (1948)
45. LORD, M. P., AND WRIGHT, W. D., *Nature*, **162**, 25 (1948)
46. LORD, M. P., AND WRIGHT, W. D., *Nature*, **163**, 803 (1949)
47. HARTRIDGE, H., AND THOMSON, L. C., *Brit. J. Ophthalmol.*, **32**, 581-91 (1948)
48. HARTRIDGE, H., AND THOMSON, L. C., *J. Physiol. (London)*, **107**, 25P (1948)
49. LORD, M. P., *Proc. Phys. Soc. (London)*, **69**, 489-93 (1948)
50. GERNANDT, B., *Acta Physiol. Scand.*, **17**, 150-60 (1949)
51. GERNANDT, B., *Acta Physiol. Scand.*, **18**, 19-25 (1949)
52. DONNER, K., *Experientia*, **5**, 413 (1949)
53. DONNER, K. (Doctoral thesis, In press)
54. GERNANDT, B., *J. Neurophysiol.*, **10**, 303-8 (1947)
55. GRANIT, R., *Acta Physiol. Scand.*, **18**, 281-94 (1949)
56. KARPE, G., *Acta Physiol. Scand., Suppl.*, **10**, 116 pp. (1945)
57. MONNIER, M., *Electroencephal. Clin. Neurophysiol.*, **1**, 87-108 (1949)
58. MOTOKAWA, K., AND MITA, T., *Tôhoku J. Exptl. Med.*, **40**, 298-320 (1941)
59. MOTOKAWA, K., AND MITA, T., *Tôhoku J. Exptl. Med.*, **42**, 114-33 (1942)
60. MOTOKAWA, K., *Tôhoku J. Exptl. Med.*, **43**, 371-82 (1942)
61. MOTOKAWA, K., *Jap. J. Med. Sci., Biophys.*, [III]**8**, 135-47 (1942)
62. MOTOKAWA, K., AND MITA, T., *Jap. J. Med. Sci. Biophys.*, [III]**9**, 23-35 (1943)
63. MOTOKAWA, K., AND MITA, T., *Tôhoku J. Exptl. Med.*, **48**, 267-84 (1945)
64. TANSLEY, K., *Ophthalm. Lit.*, **3**, 382-98 (1949)
65. KARPE, G., AND TANSLEY, K., *J. Physiol. (London)*, **107**, 272-79 (1947)
66. WULFF, V. J., *J. Cellular Comp. Physiol.*, **32**, 31-43 (1948)
67. WULFF, V. J., AND FREYBURGER, S. W., *Anat. Record.*, **101**, 665 (1948)
68. LE GRAND, Y., *Intern. Com. Illumination, Rept. No. 4* (Paris, 1948)
69. HARTRIDGE, H., *Brit. Assoc. Adv. Sci., Rept.* (Brighton, Sept., 1948)
70. HARTRIDGE, H., *Science*, **108**, 395-404 (1948)
71. HARTRIDGE, H., *J. Physiol. (London)*, **107**, 20P (1948)
72. HARTRIDGE, H., *J. Physiol. (London)*, **107**, 15P (1948)
73. THOMSON, L. C., *J. Physiol. (London)*, **108**, 78-91 (1949)
74. DE VRIES, H., *Physica*, **14**, 367-80 (1948)
75. STILES, W. S., *J. Optical Soc. Am.*, **36**, 491-92 (1946)
76. DE VRIES, H., *Physica*, **14**, 319-48 (1948)
77. SEGAL, J., *Compt. rend. soc. biol.*, **142**, 420-22 (1948)
78. JUDD, D. B., *J. Optical Soc. Am.*, **39**, 252-56 (1949)
79. CHAPANIS, A., *J. Optical Soc. Am.*, **39**, 242-49 (1949)
80. HECHT, S., SHLAER, S., SMITH, E. L., HAIG, C., AND PESKIN, J. C., *J. Gen. Physiol.*, **31**, 439-72 (1948)

81. AJO, A., AND TERÄSKELI, H., *Acta Ophthalmol.*, **15**, 374-88 (1937)
82. FLAMANT, F., AND STILES, W. S., *J. Physiol. (London)*, **107**, 187-202 (1948)
83. IVANOFF, A., *Compt. rend.*, **227**, 234-36 (1948)
84. HECHT, S., SHLAER, S., AND PIRENNE, M. H., *J. Gen. Physiol.*, **25**, 819-40 (1942)
85. BOUMAN, M. A., AND VAN DER VELDEN, H. A., *J. Optical Soc. Am.*, **38**, 570-81 (1948)
86. OTERO, J. M., PLAZA, L., AND SALAVERRI, F., *J. Optical Soc. Am.*, **39**, 167-72 (1949)
87. BAUMGARDT, E., *Arch. sci. physiol.*, **1**, 257-74 (1947)
88. BAUMGARDT, E., *L'Anné Psychol.*, 57-75, 1944/45
89. THOMSON, L. C., *J. Physiol. (London)*, **106**, 368-77 (1947)
90. AUERSWALD, W., *Ophthalmologica*, **117**, 104-9 (1949)
91. TEN DOESSCHATE, J., *Ophthalmologica*, **117**, 110-15 (1949)
92. HAIG, C., *Federation Proc.*, **8**, 65 (1949)
93. BAKER, H. D., *J. Optical Soc. Am.*, **39**, 172-79 (1949)
94. GRAHAM, C. H., BAKER, K. E., HECHT, M., AND LLOYD, V. V., *J. Exptl. Psychol.*, **38**, 205-23 (1948)
95. ZEGERS, R. T., *J. Psychol.*, **26**, 477-98 (1948)
96. GRAHAM, C. H., RIGGS, L. A., MUELLER, C. G., AND SOLOMON, R. L., *J. Psychol.*, **27**, 203-7 (1949)
97. GRAHAM, C. H., HAMMER, E. R., MUELLER, R. D., AND MOTE, F. A., *J. Psychol.*, **27**, 209-16 (1949)
98. RATOOSK, P., *Proc. Natl. Acad. Sci. U. S.*, **35**, 257-59 (1949)
99. MUELLER, C. G., AND LLOYD, V. V., *Proc. Natl. Acad. Sci. U. S.*, **34**, 223-27 (1948)
100. LIT, A., *Am. J. Psychol.*, **62**, 159-81 (1949)
101. BIRUKOW, G., *Z. vergleich. Physiol.*, **31**, 322-47 (1949)
102. HOUSTOUN, R. A., *Proc. Roy. Soc. (London)*, [A], **82**, 606 (1909)
103. RUSHTON, W. A. H., *Nature*, **164**, 743 (1949)
104. MOTOKAWA, K., *J. Neurophysiol.*, **12**, 291-303 (1949)
105. SJÖSTRAND, F., *J. Cellular Physiol.*, **33**, 383-404 (1949)
106. COLLINS, F. D., AND MORTON, R. A., *Nature*, **164**, 528 (1949)

# METABOLIC FUNCTIONS OF THE ENDOCRINE GLANDS<sup>1</sup>

BY JAY TEPPERMAN AND HELEN M. TEPPERMAN<sup>2</sup>

*Department of Pharmacology, Syracuse University College of Medicine*

## METHOD AND SCOPE

Approximately 600 references that appeared to pertain to the subject under review were collected from July 1948 to June 1949. Of these, the reviewers were able to read and abstract about 490, and to attend illustrated presentations of many of the papers cited as abstracts. The following review contains references to less than one third of the endocrine papers of which we became aware during the year. As in the past, the selection has been quite arbitrary, and no assay of "significance" is implied in either the inclusion or exclusion of individual reports.

## ANTERIOR PITUITARY

*Mechanisms of activation of pituitary trophic hormones.*—While each trophic hormone-end organ complex constitutes a functional unit and can profitably be discussed as such (1), the reviewers prefer to classify certain reports in the domain of pituitary physiology primarily. The nature of the chemical stimuli which provoke increased rates of production and release of the individual trophic hormones from the hypophysis is being actively discussed, and many analogies between the modes of activation of various trophic hormones are being considered.

Anderson & Haymaker (2) have published an excellent review of the influence of the hypothalamus on sexual function. They evaluate the evidence for neural or neurohumoral links between the hypothalamus and the anterior hypophysis, considerations which are of great importance with respect to nongonadotrophic

<sup>1</sup> From the Department of Pharmacology, Syracuse University College of Medicine, Syracuse, N. Y. The authors gratefully acknowledge help received from the Librarians of the College of Medicine, Miss Janet DeWitt and Mrs. Sally Benforado.

<sup>2</sup> This work was done during the tenure of grants from the American Cancer Society (administered by the Committee on Growth of the National Research Council) and the Hendricks Fund of the Syracuse University College of Medicine.

hormones as well as gonadotrophic ones. Hillarp (3) produced lesions in various regions of the hypothalamus of female rats and concluded that a center controlling luteinizing hormone (LH) secretion exists in the anterior hypothalamic area just anterior and ventral to the paraventricular nucleus. Harris (4), on the basis of experiments involving an ingenious remote-control method of stimulation, rejects the hypothesis that impulses travel from the hypothalamus to the anterior pituitary by way of the infundibular stem. He stresses the importance of the hypophysial portal vascular system he had previously described with Green. However, Brolin (5) asserts that changes that occur in anterior pituitary basophile cells following thyroidectomy do not occur in completely stalk-sectioned rats.

Following the lead of Markee *et al.* (6), whose careful studies indicate an adrenergic neurohumoral link between ovulatory stimulus and pituitary LH release, experimenters continue to explore the role of epinephrine or adrenergic nerve stimulation in the release of a number of pituitary trophic hormones. Sawyer and co-workers (7) reported that atropine blocks postcopulation ovulation in rabbits when injected a few seconds after copulation. They suggest, therefore, that a cholinergic link participates in the neurogenic stimulus to ovulation and compare their findings with the mechanism of the induction of epinephrine secretion in the adrenal medulla. Nickerson (8) criticized the interpretation of the results of experiments in which the adrenergic blocking agent dibenamine was used to block the neurogenic stimulus to ovulation on the grounds that the block may have been a nonspecific one related to the transitory central nervous system excitant properties of dibenamine. To rule out this possibility, he suggested using 2-dibenzylaminoethanol, a dibenamine hydrolysis product which retains the central nervous system stimulant properties of the parent compound but lacks its adrenergic blocking power. Acting on this suggestion Sawyer *et al.* (9) showed that 2-dibenzylaminoethanol did not block ovulation although it did produce profound central nervous system excitation.

The role of epinephrine in adrenocorticotrophic hormone (ACTH) release, a subject which has been discussed in previous reviews of this series, has been considered by a number of workers. Tepperman & Bogardus (10), using the adrenal ascorbic acid depletion test, were unable to demonstrate a block in ACTH out-

put following the administration of either dibenamine or the autonomic ganglion blocking agent tetraethylammonium chloride. In fact, they showed that the injection of dibenamine itself produced a fall in adrenal ascorbic acid concentration. Paschkis and others (11, 12) confirmed both the facts that dibenamine produced an ACTH discharge and that it did not prevent an additive effect following formalin and insulin injection. However, Seifter *et al.* (13) published a preliminary report to the effect that the histological changes of the "alarm reaction" in the thymus and the adrenals provoked by epinephrine were reversed by dibenamine, but those provoked by colchicine were not. In unpublished experiments suggested to the reviewers by Wolfson (14), we have failed to demonstrate a block of ACTH secretion in rats treated with ergotamine tartrate, a drug which is known to prevent the rise in uric acid secretion which follows epinephrine injection (15) and also blocks the glycogenolytic action of epinephrine *in vitro* (16).

Soffer and his co-workers (17) present evidence to show that epinephrine, under some circumstances, may enhance the pituitary output of thyrotrophic hormone. Thus, the injection of epinephrine is almost equivalent to the sudden opening of a trap door under the pituitary with an outpouring of trophic hormones of every size and description. While epinephrine and adrenergic nerve stimulation may play a part in the excitation of certain trophic hormonal responses, many subtle aspects of this general problem remain to be studied and described and other points of view should be vigorously explored. For example, Ellinger (18) believes that the irradiation of a sufficiently large volume of the body results in the release of histamine-like substances which may cause the anterior pituitary to secrete corticotrophic hormone. This hypothesis deserves testing in animals pretreated with antihistamine drugs.

Sayers and his colleagues continue their imaginative studies on ACTH release. They have found that 24 hr. after adrenalectomy, the pituitary ACTH content was reduced by 80 per cent, as compared with 27 per cent in sham-operated rats. Desoxycorticosterone injection prevented a considerable part of the reduction in adrenalectomized animals (19) and also, in intact animals, produced a state of insulin sensitivity which the authors are inclined to attribute to a direct inhibitory action on ACTH output. These data are difficult to interpret since, as with every study of chemical morphology, there is no measure of hormone production rate from

the time of experimental manipulation to the time of death of the animal. Also, one wonders about the physiologic significance of desoxycorticosterone inhibition of the hypophysis in the rat in the light of the studies of Deane and her colleagues (20, 21, 22), who feel that in that species, at least, the zone of the adrenal cortex that produces desoxycorticosterone-like materials is not under hypophysial control. It is of some interest, in this connection, that D'Angelo (23) could not block the adrenal enlargement of starvation by giving liberal quantities of aqueous adrenal cortical extract.

The general view expressed by Sayers and his associates, that trophic hormone output is regulated by the level of circulating target organ hormone, has had a longstanding appeal, but experimental support for it has not been abundant. Two papers published during the current year are concerned with this problem. In one, Gaarenstroom & De Jongh (24) studied the gonadotrophic potency of the hypophyses of estrogen treated rats and, on the basis of their ingenious analysis, concluded that estrogen lowers the prolactin content of the pituitary. McQuillan *et al.* (25) found no thyrotrophic hormone in the pituitaries of thyroxine-treated cattle as contrasted with control glands which contained appreciable amounts of the hormone.

The question of whether the pituitary content of a trophic hormone is an accurate index of the amount of hormone released into the blood stream is the basis of a report by Meites & Reed (26), who studied the pituitary content of gonadotrophin and lactogen in intact and ovariectomized rats subjected to varying degrees of inanition. They found no reduction in gonadotrophic hormone content in spite of marked atrophy of the ovaries and uteri of the intact rats and the high initial content of the pituitaries of the gonadectomized animals. There was, however, a significant decrease in the pituitary lactogen content of mother rats starved during lactation. The authors suggest that, in this case, pituitary gonadotrophic hormone content is not an accurate reflection of the amount of hormone released into the blood stream, whereas the low lactogenic content signifies a low level of release. It is entirely possible, though not likely, that the low lactogen content might indicate an increased rate of production and release of the hormone as a compensatory reaction for failure of the milk-secreting end organ incident to starvation. In this connection, Rinaldini (27)

found the gonadotrophic potency of the pituitaries of starved rats much higher than that of normally nourished ones. He concludes that gonadotrophins accumulate in the anterior lobe during inanition and that the release of these hormones may be restricted in the starved animal.

In addition to examples already cited in other connections, there have been a number of reports which have considered the excitation or inhibition of single pituitary trophic hormones. Since there are only three types of cells in the anterior pituitary gland, certain cells must elaborate a number of trophic hormones, although there is still no great unanimity of opinion about the cell source of the individual substances (for example, see 28 and 29). Certain authors have described conditions in which they suggest that one trophic hormone may be produced and released preferentially at the expense of others. For example, Szego & White (30) found that the mobilization of nitrogen from lymphoid tissue was diminished in castrated mice of both sexes, and they suggest that the high level of gonadotrophin production incident to castration may have compromised the ability of the pituitaries of their animals to respond to inanition by an increase in ACTH output. Edelman (31) thinks the gonadal atrophy seen after whole body radiation may be due to a reverse "crowding out" of gonadotrophin production and release by a heavy demand for ACTH. Mellgren (32) similarly suggests that pituitary basophiles may make ACTH preferentially at the expense of both gonadotrophic and thyrotrophic hormone (TH) output. It should be pointed out that, in the case of cold exposure at least, there is an increased output of both ACTH and TH.

*Effects of trophic hormones on their respective end organs.*—Although it has often been said that hormones regulate rates of chemical reactions in cells but do not initiate them (for example, see 33), the anterior pituitary trophic hormones certainly appear to initiate chains of chemical reactions in the end organs of hypophysectomized animals. The chemical potential for hormone synthesis exists in the end organ cell, but it functions effectively only when the circuit is completed by the trophic hormone switch.

In addition to the seminal studies of Sayers and his colleagues [see Long (34)] on fluctuations in adrenal cholesterol produced by ACTH administration, three groups of investigators have explored the possibility that changes in the cholesterol content of the gonads

might be demonstrated following the administration of gonadotrophic hormones. Everett's beautiful study (35) clearly showed that deposition and disappearance of cholesterol in the rat corpus luteum could be produced by injecting pituitary LH and lactogen in appropriate sequence and dosage. Similarly, Tepperman & Tepperman (36) found that the cholesterol ester concentration of the immature rat testis could be changed by the administration of certain trophic hormones. Levin & Jailer (37) described fluctuations in the cholesterol content of the immature rat ovary following the injection of chorionic gonadotrophin or pregnant mare's serum (PMS). Claesson, Hillarp and their colleagues (38, 39, 40) have been engaged in a related histochemical study of the ovaries of rats and guinea pigs.

All of these investigators appear to be agreed that stored cholesterol, and especially the esterified form, is the probable precursor of the steroid hormones, and that the trophic hormones stimulate the production of biologically active steroids. That they do so by virtue of a biocatalytic action is indicated by the fact that they are effective in microgram quantities. Whether they act on the energy-yielding reactions which are coupled with the synthetic ones, as suggested by the work of Gemzell (41) and by Vogt's adenosinetriphosphate (ATP) experiment (42), or whether they participate in crucial steroid interconversion reactions are questions that will be answered by future studies.

*Growth hormone.*—Increasing amounts of purified growth hormone are becoming available for a rapidly mounting number of physiologic studies. The new preparative technique of Wilhelmi and his colleagues (43, 44) will certainly stimulate further work with this hormone. The New Haven workers have obtained the astonishingly high yield of 33 gm. of growth hormone per kg. of fresh anterior pituitary gland.

In a series of reports (45 to 48), the effects of purified growth hormone have been quantitatively determined in intact and hypophysectomized rats. As little as 30  $\mu$ g. per rat per day produced a significant retention of nitrogen in the hypophysectomized rat (45). Studies on adult female rats at higher dose levels showed a transient period of nitrogen retention followed by a period of refractoriness to low doses but not to higher ones (46). The nature of this progressively increasing requirement for exogenously administered hormone is not known. In agreement with the results

of previous experiments with whole anterior pituitary extract, growth hormone produces an increase in protein and water content and a decrease in body fat (47).

Chow & Greep (49) noted that hypophysectomized rats on a crude casein diet treated with purified growth hormone grew better than did those on diets containing purified proteins. This observation suggests the possibility that growth hormone was able to bring into relief a deficiency of the purified diets which were apparently complete for untreated rats.

Students of the growth hormone have been interested in such apparently diverse subjects as the use of serum phosphorus as a measure of growth hormone activity (50 to 53), the effect of the hormone on liver lipids and ketonemia (54, 55, 56), studies on osteogenesis and calcification (57, 58, 59), renal function (60, 61), and on blood amino acid levels (62, 63). There have been a few additional attempts (64, 65, 66) to discover a biochemical locus of action of the hormone in order to provide a common denominator for current and future physiological studies. On the basis of their studies of tissue arginase activities Kochakian & Stettner (65) believe that the protein anabolic effects of growth hormone and testosterone propionate involve different intermediary metabolic processes. In fact, they demonstrated some inhibition of the usual increase in kidney arginase activity resulting from testosterone injection when growth hormone was given with the testosterone.

An excellent review by Li (67) emphasizes the interrelationships between the pituitary trophic hormones as they affect growth and summarizes the evidence in favor of the protein anabolic function of the growth hormone. Further aspects of the growth hormone problem will be considered in the section on INSULIN AND EXPERIMENTAL DIABETES.

#### ADRENAL CORTEX

*Site of production of steroid hormones.*—The careful histochemical studies of Deane and her colleagues on rat adrenals (20, 21, 22) support the view that the *zona glomerulosa* is the source of desoxycorticosterone-like products whereas the 11-oxygenated steroids arise from the *zona fasciculata*. Moreover, in experiments (20) in which a dietary reduction in the sodium:potassium ratio was induced in hypophysectomized rats, changes in the *zona glomerulosa* suggesting "increased activity" were observed, while no such

changes were seen in the *fasciculata*. After enucleation of the adrenal (22) the regenerated cortex shows a normal zonation of secretory activity and forms both "sugar" and "salt" hormone. In subsequent studies (21) on the effects of pituitary ACTH on the intact rat, the results indicated that the ACTH stimulated the *fasciculata* to produce 11-oxygenated steroids, but failed to enhance the output of salt-retaining steroids by the glomerulosa. The authors refer to a number of reports (to which one may now add 68, 69) of the occurrence of salt retention following the administration of ACTH to man, and suggest the possibility of a species difference between man and the rat in this regard (See section on *The rheumatic diseases*). The finding by Dempsey *et al.* (70) that alkaline phosphatase persists in the *zona glomerulosa* after hypophysectomy but disappears from the *zona fasciculata* offers additional suggestive evidence that the former may not be under direct hypophysial control in the rat.

The results of other studies (71 to 74), in general, agree with the findings cited above. Of particular interest to the authors is the report of Bourne (75), who examined the histologic structure of the adrenals of 250 species and found that, in certain of them, the well-recognized cortical zones cannot be distinguished. It would be informative to study the responses of unzoned adrenal cortices to purified ACTH administration.

A number of reports published during the period of review were concerned with interrelationships between the adrenal cortex and the sex steroids. Jones (76, 77) has studied the adrenal x-zone problem in mice of both sexes. He suggests that testosterone causes disappearance of the x-zone in males at puberty, and that chorionic gonadotrophin may accomplish the same result in females on the occasion of the first pregnancy. However, he implies that pituitary LH maintains the integrity of the x-zone in hypophysectomized female animals. Does this constitute a functional differentiation between pituitary LH and chorionic gonadotrophin? On the other hand, Leathem (78) was not impressed by the constancy of the disappearance of the x-zone in animals treated with pregnant mare's serum gonadotrophin (PMS). Jones (77) observed further that the x-zone was negative to those histochemical tests for which the permanent cortex and other steroid producing organs are characteristically positive. "This," he says, "is in agreement with the view that a steroid type of hormone is not secreted by the x-zone."

Other studies on gonad-adrenal interrelations include those of the androgen- or estrogen-secreting adrenal cortical tumors which develop in Bagg strain mice following gonadectomy of either sex (79, 80). Postgonadectomy nodular hyperplasia of the adrenals in Syrian hamsters has been prevented by the administration of testosterone propionate to either sex (81). In addition, Cowie (82) made a careful study of the influence of age and sex on the life span of adrenalectomized rats. He found that mature female rats outlive male rats by four to five days after adrenalectomy, and he is inclined to attribute this prolongation of survival to the presence of progesterone in the females. Finally, Katsh *et al.* (83) described the prevention of seminal vesicle atrophy in adult rats bearing adrenal autotransplants on a seminal vesicle. These transplanted glands were not well differentiated into zones and the authors feel that the products of their secretory activity may differ from those of normal adrenals *in situ*.

*Metabolism of the adrenal cortex.*—Srere *et al.* (84) reported that beef adrenal tissue *in vitro* can convert  $C^{14}$  of doubly-labelled acetate to cholesterol. This interesting finding has raised a host of important questions. First, one would like to know whether the rate of conversion of acetate to cholesterol is sufficiently rapid to supply the secretory needs of the gland at rest and under conditions in which the hormonal output may be increased by a factor of six or more. Then, since practically all of the fluctuations in adrenal cholesterol in association with increased hormone output have been observed to occur in the ester fraction, it would be of interest to determine whether or not cholesterol produced in the gland is esterified there as well. Conn & Vogel (85) described pertinent changes in the esterified cholesterol in serum of patients treated with purified pituitary ACTH. On the basis of their findings these investigators believe that the rate of esterification of cholesterol may more sharply limit the secretory performance of the adrenal than the rate of cholesterol synthesis. These are fascinating subjects for future inquiry, involving, as they do, the very old clinical question of the mechanisms involved in apparent disturbances of the physiology of steroid-producing glands in chronic liver disease (86).

Two brief reports of the production of adrenal steroids by isolated perfused adrenal tissue have appeared. Vogt (42), who perfused dog adrenal with blood and assayed for cortical activity

by a cold exposure test in adrenalectomized rats, found a considerable output of the "resting" gland and was able to demonstrate a marked increase in "cortical hormone" output when ACTH was added to the perfusate. The secretion was also enhanced by ATP, creatine phosphate, and by marked increases in the potassium concentration of the perfusate. The reader awaits a more detailed account of these experiments with great interest.

Hechter (87) perfused beef and sheep adrenal glands with homologous citrated blood and measured both formaldehydogenic substances (FS) and glycogenic activity of the effluent from the glands. He was able to detect significant amounts of FS only after ACTH administration. Moreover, one infers that there was no parallelism between increased FS and increased glycogenic activity measured against a Kendall Compound E Standard.

Gemzell (41) has described an increase in the turnover rate of radioactive phosphate in the acid soluble organic phosphate compounds of the adrenal cortex following injection of ACTH. These changes are associated with the well-known changes in cholesterol ester concentration in the gland and with evidence of an increased output of cortical hormones. The author states that the metabolism of phosphorus is an indication of carbohydrate metabolism and infers that the trophic hormone may act by stimulating carbohydrate metabolism. It is noteworthy in this connection that Vogt (42) was unable to demonstrate enhanced secretion of cortical hormone by the isolated adrenal by adding glucose to the medium, and that Kodama (88) found the presence of 0.2 per cent glucose in the medium depressed the oxygen consumption of rabbit adrenal cortical slices *in vitro*. Vogt's finding augmentation of adrenal cortical secretion by ATP clearly indicates a coupling of energy-yielding reactions with hormone production and release. However, the high fat content of the gland suggests that Gemzell's studies might be extended profitably to include turnover rate of phospholipid phosphorus.

The interest of students of adrenal physiology in ascorbic acid continues. Dugal & Thérien (89) made the interesting observation that the injection of large doses of ascorbic acid completely prevented the adrenal hypertrophy that is commonly seen following cold exposure in the rat. Moreover, resistance to cold was increased in the ascorbic acid-treated animals. Certainly this cortical hormone-sparing action of vitamin C deserves further study.

That the fluctuations in the ascorbic acid content of the adrenal with sudden changes in secretory activity may not be peculiar to that organ is suggested by the study of Hoch-Ligeti & Bourne (90). These authors found periodic variations in the concentration of ascorbic acid in the ovaries and liver and in the histological distribution of the material in the adrenals in association with the oestrus cycle. These studies, together with that of Miller & Everett (91), who demonstrated a marked lowering of the ascorbic acid concentration of the corpus luteum of the LH-primed, lactogen-treated rat, support the view that ascorbic acid participates in some type of reaction which does not occur exclusively in the adrenal cortex. The high concentration of the vitamin in steroid-producing (adrenals, gonads), steroid-inactivating (liver), or steroid-sensitive (pituitary) organs suggest that steroid interconversion may be the common denominator of this specialized function of ascorbic acid.

A new study (92) of the requirement for pantothenic acid by the adrenalectomized rat revealed that the amount of the vitamin necessary to prolong the survival time of salt-maintained adrenalectomized rats is much greater than that required to maintain optimal growth in intact rats of the same age. The mechanisms involved in this partial compensation for adrenal deprivation in the pantothenic acid-treated animals are not known.

In the past there has been some disagreement about the effect of high protein diets on the size and activity of the adrenal glands (93 to 96). Recently, Selye (97) has reviewed the evidence in favor of the view that such diets do not, per se, cause adrenal hypertrophy. They do, however, cause an augmentation of hypertrophy in "stressful" circumstances. If high protein diets should enhance the response to purified ACTH as they did to crude anterior pituitary extract (93), particularly in the hypophysectomized animal, the potentiating action of these diets will resolve itself into a problem of adrenal cortical metabolism rather than one concerned with the production and release of ACTH.

*The adrenal cortex and protein metabolism.*—In a series of reports (98 to 101) Engel and his colleagues have discussed the nature of the protein catabolic response to adrenal cortical extract (ACE). Having presented their method (98) for studying rapid changes in nitrogen metabolism by measuring the rate of urea accumulation in the nephrectomized rat, the authors describe augmentation of

urea formation following ACE injection and the prevention of this response by glucose (99). An amino acid mixture plus ACE produced no greater urea accumulation than did either alone. Salt-poor human albumin administration caused no change in urea formation, but when given with ACE there was a greater accumulation than with ACE alone. This effect, too, was abolished if glucose was given with the albumin. In agreement with previous findings (102), no defect in deamination was found in adrenalectomized-nephrectomized rats (100), and urea formation following the administration of rat plasma was increased only if ACE was given before the plasma. When insulin hypoglycemia was used as a maneuver to accentuate carbohydrate lack, ACE produced a very great augmentation of urea formation (101).

Engel and his colleagues conclude that the site of action of adrenal cortical hormone in protein metabolism is on "whole protein rather than amino acids" and that the increase in protein catabolism following ACE can be inhibited either by administering glucose or amino acid mixtures. They discuss the possibility that protein breakdown is not an obligatory action of ACE, but that it may be secondary to events that occur primarily in the metabolism of the other major foodstuffs. Young *et al.* (103), for example, describe defective glycogenesis in patients with gastric cancer. When these patients were given ACE and glucose (a circumstance that would preclude the possibility of enhanced gluconeogenesis, according to the hypothesis of Engle *et al.*) glycogenesis was markedly increased. Although the question of variable intestinal absorption rates was not ruled out in these experiments, the possibility remains that ACE participated in the increased rate of glycogenesis from glucose.

Awapara *et al.* (104), on the basis of a chromatographic separation of liver and muscle amino acids into dicarboxylic, glycine and alanine cautiously suggest that Kendall's Compound E promotes carbohydrate synthesis by way of a transamination system. Whether or not this is true the authors certainly have demonstrated marked differences in the dicarboxylic acid concentration in Compound E treated rats as compared with controls and it is possible that these changes may be secondary to primary effects on the intermediate reactions of carbohydrate metabolism.

The studies on nephrectomized rats cited above are not consistent with the suggestion of Noble & Toby (105) who maintain

that the effect of adrenalectomy on nitrogen excretion may be entirely renal. It is difficult to accept the statement: "It seems certain that an increased secretion of adrenal hormones does not improve the tolerance of a normal animal to traumatic procedures, nor is it necessary for the breakdown of protein." Kline (106) demonstrated that adrenalectomized dogs showed no increase in arteriovenous difference of plasma amino acid nitrogen following hemorrhage, in contrast to controls. This constitutes good circumstantial evidence that the adrenalectomized animal is unable to mobilize endogenous nitrogen at a normal rate in a stressful situation. In addition, White and his co-workers (107) studied the rate of incorporation of  $N^{15}$  (injected as glycine) into certain selected tissue and serum proteins. They demonstrated a more rapid incorporation of the labelled nitrogen in fasted-adrenalectomized rats than in fasted normal ones, and they suggest that this result confirms the hypothesis of a retardation in protein catabolism incident to adrenalectomy. Liver regeneration in adrenalectomized rats on a high protein diet was consistently more rapid than that of normal controls (108), a fact which supports the general hypothesis of the ascendancy of protein anabolism over catabolism in the adrenalectomized animal.

After demonstrating marked thinning of the skin and reduced hair growth in rats treated with ACTH (109), Baker and others applied adrenal cortical hormones directly to the skin and demonstrated marked inhibition of growth of skin and hair. Thus, these substances may inhibit growth directly without the mediation of another gland. In the light of Engel's findings, discussed herein, it would be of interest to apply Baker's techniques to normally fed, underfed and overfed animals.

*Fat metabolism.*— Two reports (110, 111) describe an increase in liver fat content after injection of ACTH. In one of them (110) Levin points out the fact that accumulation of liver fat in the rat is not a constant finding following exposure to all types of stress. Cold exposure and severe exercise cause an increase in liver fat but exposure to low barometric pressure does not. Parenteral treatment with glucose during exposure to an otherwise effective stress or during treatment with pituitary extract, prevents fat accumulation in the liver, a fact which is reminiscent of the inhibition of the protein catabolic effect of ACE by glucose (99).

Several related studies on ketone body production have

appeared during the year. Bennett *et al.* (112) reported that 100 mg. daily of Kendall's Compound E acetate caused a significant elevation in the blood ketone level in patients with Addison's disease. A similar experiment was performed in the normal female dog (113) with comparable results. These findings could have resulted either from increased production or an inhibition of oxidation of ketone bodies. Bondy & Wilhelmi (114) were unable to demonstrate significantly depressed rates of ketone body formation *in vitro* by liver slices obtained from adrenalectomized rats, but slices obtained from hypophysectomized rats made significantly fewer ketone bodies than did those of normal animals.

*The adrenals and intracellular enzymes.*—Folley & Greenbaum (115) showed that rats adrenalectomized on the fourth day of lactation, with necropsy on the 17th day, showed less arginase activity of liver, kidney, and mammary gland than did sham-operated, pair-fed controls. However, according to Kochakian (116) treatment with lipo-adrenal extract did not change the liver arginase activity although the alkaline phosphatase activity of liver was markedly increased. Cowie *et al.* (117), aware of the possibility that the change in mammary gland arginase activity after adrenalectomy could well be a nonspecific effect of adrenal deprivation, measured the  $Q_{O_2}$  of mammary gland slices of adrenalectomized animals and suitable inanition controls. They found no significant difference between the two groups and therefore suggest that, since the arginase activity of the adrenalectomized rats' tissue was much reduced under these circumstances, a particularly intimate relationship exists between the adrenal cortex and tissue arginase. The reviewers feel that a glucose  $Q_{O_2}$  does not constitute a sufficiently rigorous test of the integrity of the many individual enzymatic stages of carbohydrate oxidation. It is entirely possible that serious specific defects in carbohydrate metabolism may be produced by adrenalectomy, and that these defects may be brought into relief only by forcing particular enzyme systems to work at their capacity.

*The rheumatic diseases.*—The most dramatic announcement of the year concerning the subject under review was made by Hench, Kendall, and their collaborators (118 to 121) when they reported that the administration of Kendall's Compound E to patients with rheumatoid arthritis produced a marked amelioration of their symptoms and signs. After pointing out that spontaneous remis-

sions of the disease occur commonly in a variety of circumstances (notably in association with jaundice and pregnancy) the Mayo Clinic investigators suggested the possibility that a common "temporary remission factor" may be found in the many apparently unrelated conditions in which remissions occur (118). In every one of 14 patients with severe rheumatoid arthritis given large doses of Compound E (at least 100 mg. daily) for various lengths of time (119) articular and muscular symptoms were markedly improved and the sedimentation rates were lowered. Two patients given ACTH showed a similar response, but in all 16 patients the improvement was apparent only during the period of administration of the drug. Moreover, in three young patients with rheumatic fever (120) there was marked clinical improvement which the authors conservatively attribute to Compound E treatment. Most striking to the reviewers was the prompt return of prolonged P-R intervals and sedimentation rates to normal values. The authors admit that the pattern of improvement in the patients with rheumatic fever "seems more definite and distinctive than it would otherwise" in the light of previously observed responses of patients with rheumatoid arthritis. They also express the hope, engendered by their observations of the responses of muscles of rheumatoid arthritis patients, that treatment with Compound E may eventually prove to protect the myocardium and heart valves from damage during the active phase of the disease.

This series of papers has been acclaimed by competent critics as one of the most important advances in experimental medicine of recent years, and there is no doubt that these findings will stimulate incalculable advances, not only in the field of the rheumatic diseases, but in those of hypertensive vascular disease and renal disease as well. No suggestion has been made concerning a possible mechanism of action of Compound E in ameliorating the symptoms of the diseases discussed above. Selye and his colleagues (122) have described the production of arthritic lesions in rats by the administration of desoxycorticosterone acetate, and the same author (123) advances the hypothesis that shifts in the hormonal pattern of the adrenal cortex may occur in association with the adaptation syndrome. Are the joint symptoms of rheumatoid arthritis in part a reflection of an overproduction of a salt-water corticoid? The increase in circulating blood volume of certain

patients with rheumatoid arthritis is consistent with this possibility (123). It is possible that the 11-oxygenated steroid may redress the balance of cortical hormone production by inhibiting the output of desoxycorticosterone. It may act as a competitive inhibitor of desoxycorticosterone at the end-organ, a theory which is strengthened by the fact that rather large doses of Compound E are necessary for a therapeutic effect. It almost certainly does not act by inhibiting pituitary production of ACTH, since ACTH itself is effective—a presumptive argument, by the way, that, in the arthritic human being as in the rat, ACTH elicits an adrenal cortical secretion which is predominantly composed of 11-oxygenated steroids. One must also mention the possibility, suggested by the report of Opsahl (124), that at least part of the beneficial effect of Compound E may be related to its antihyaluronidase properties.

According to Hellman (125), attacks of gouty arthritis follow a relative decrease in adrenal cortical activity and are relieved by increased adrenal activity. The relief of symptoms in gout may be related to the relief experienced by patients with rheumatoid arthritis or to a specific effect of ACTH on purine metabolism.

*Response to stress.*—Reports continue to be published on the ability of cortical extract or cortical steroids to protect adrenalectomized animals against various types of stress. Lewis & Page (126) have continued their work on the protection of adrenalectomized animals against various toxins afforded by cortical hormones. In general, they have found that the protective power of adrenal hormones parallels their effect on carbohydrate metabolism. However, in the experiments reported here a synergism between Compound A and desoxycorticosterone in protecting adrenalectomized rats against typhoid vaccine was observed. Ingle & Nezamis (127) have succeeded in restoring to normal the work capacity of adrenal deficient rats by constant intravenous injection of cortical extract. The same authors (128) found that glucose infusions did not improve the work performance of adrenalectomized rats unless cortical extract was also given. They are puzzled by the capacity of hormones, presumably concerned with inhibition of carbohydrate utilization, to sustain work capacity and suggest that the hypoglycemic tendency of adrenalectomized animals may be due partially to a failure to mobilize and utilize fat and protein for energy purposes.

There have been many attempts to increase the capacity of animals with intact adrenals to withstand stress by giving cortical hormones or ACTH. Most such attempts have been unsuccessful. Thus, Leger *et al.* (129) found ACTH incapable of affording protection against anaphylactic shock. Tobian & Strauss (130) reported cortical extract to be without effect on the recovery from pneumococcal infection of penicillin-treated mice, and Ingle *et al.* (131) could not influence the work capacity of normal rats by treatment with cortical extract. However, Dureuil *et al.* (132) found that the work capacity of some normal rats previously exposed to extreme heat could be improved by cortical hormone. The authors interpret their results to mean that some factor other than cortical hormones is necessary for the action of these hormones and that this factor is released as a result of the heat stress. It seems probable that their results could be explained by assuming that the heat exposure so increased the demand for cortical hormone that the animals were suffering from temporary adrenal insufficiency when subjected to the work test. In that event administered hormone would be repairing this deficiency as in adrenalectomized animals. Lewis & Page (126) report that adrenal extract given to animals with intact adrenals did offer some degree of protection against a particularly virulent strain of pneumococcus, though no protection against other toxins could be obtained.

The adrenal does not function in protecting rats against cold until they are 16 days old, according to Holtkamp *et al.* (133). The experiments of Covian (134) indicate that the emotional stress experienced normally by wild Norway rats, which may contribute to the relative adrenal hypertrophy and increased total adrenal cholesterol observed by Nichols (135), markedly increases the requirement for adrenal hormones by wild adrenalectomized rats of this strain as compared to laboratory rats.

#### INSULIN AND EXPERIMENTAL DIABETES

*The etiology of diabetes mellitus.*—A confluence of many separate streams of research has resulted in a bold new hypothesis concerning one mechanism by which the insulin-producing apparatus may be damaged. Lazarow (136), in a thoughtful review, traces the development of the concept that the production of alloxan diabetes, and, perhaps, of spontaneously-occurring forms of the disease as well, may be related to an enhanced vulnerability

of the beta cells of the islets of Langerhans due to a low local concentration of protective sulfhydryl compounds. He visualizes the local reduction of glutathione concentration as an expression of the need for sulfhydryl compounds in insulin synthesis. While the theory is a very attractive one, the presentation is slightly marred by the following statement (which the author makes in an effort to explain the fact that animals on a high fat diet are particularly susceptible to alloxan diabetes): "If insulin should prove to be necessary for fat oxidation, then a high fat diet might also stimulate insulin synthesis and thereby influence the susceptibility of the beta cells (to alloxan)." Many investigators believe that the rate of insulin synthesis is depressed by fat-feeding [for example (137)]. One might offer the alternative hypothesis that fat-feeding produces a sort of "disuse atrophy" of the insulin synthetic mechanism with such a marked fall in activity of the insulinogenic cells that a comparatively minor insult, added to their daily physiologic chores, is enough to damage them irreparably.

Conn and his colleagues have continued their extraordinarily interesting work with human ACTH diabetes which they began last year (138). In addition to previously reported findings they now describe (139) a fall in blood glutathione in association with ACTH administration and they state that there was a better correlation between glycosuria and diminished blood glutathione than between glycosuria and enhanced uric acid output. Their suggestion that islet damage may be related to an increased intracellular production of uric acid and alloxan-like intermediate substances gains strength from the report [quoted by Lazarow (136)] that permanent diabetes has been produced in glutathione-depleted rabbits by the injection of uric acid. Moreover, Conn and his co-workers demonstrated temporary alleviation of human ACTH-induced diabetes in man by the administration of reduced glutathione (140). The transient beneficial effects of the glutathione were related by the authors to improved renal tubular reabsorption of glucose and, possibly, improved glucose utilization. One wonders what effect, if any, the amounts of glutathione given in this experiment would have on Mirsky's "insulinase" (141). Much work remains to be done before the glutathione effect in these experiments can be equated with sulfhydryl protection against alloxan diabetes.

An analysis of the importance of the individual pituitary hormones in the diabetogenic effect of whole pituitary extract has become possible as the purified hormones have become available. Additional studies have been made of the enhancement of glycosuria in both alloxan-diabetic animals and Houssay preparations by purified ACTH (142, 143). There is general agreement, too, that purified growth hormone does not increase glycosuria under similar conditions (143, 144). Both growth hormone and ACTH, however, do increase the ketonuria of severely diabetic animals on carbohydrate-free diets (142). The possibility of the existence of a pituitary diabetogenic factor distinct from either ACTH or growth hormone continues to be a very strong one (145). Thus, the diabetogenic effect of crude pituitary extract is being revealed as an exceedingly complex one, involving, as it does, the administration of many individual hormones to animals whose tissues may be variably responsive to the individual diabetogenic principles.

*The mechanism of insulin action.*—The study of Stadie & Haugaard (146), like that of Broh-Kahn & Mirsky (147), fails to confirm many of the experimental findings, familiar to annual readers of this section, upon which the original hexokinase theory of the action of insulin was based. These workers found no significant effect of adrenal cortical extract or of adrenal cortical extract plus insulin on hexokinase activity of muscle extracts obtained from either normal or alloxanized rats. No initial lag phase of the hexokinase reaction was observed in extracts of muscle or kidney from normal or alloxanized rats. The reasons for the discrepancies between these findings and those of Cori and his colleagues (200) are apparent neither to Stadie & Haugaard nor to the reviewers. Moreover, in addition to the well-known enigma of the insulin sensitivity of the hypophysectomized animal, we now have an interesting report by Zwilling (148), who states that insulin hypoglycemia can be produced in the chick embryo before the cytological differentiation of the pituitary, adrenals, and the endocrine portion of the pancreas has occurred. One must postulate either that the mechanism of action of insulin in this circumstance differs from that in postembryonic life or that insulin does not require the presence of hexokinase inhibitors of pituitary and adrenal origin in order to exert its effect.

Two reports (149, 150) indicate that insulin stimulates the

uptake of glucose by the isolated diaphragms of both normal and hypophysectomized rats. Experiments were done long enough after hypophysectomy to make the persistence of a substance of pituitary origin in the tissue unlikely in the extreme. On the other hand, Reiss *et al.* (151) found that the  $P^{32}$  uptake of slices of gray matter of the brains of rats was increased by 50 to 400 per cent after hypophysectomy. They attribute this result to an increased rate of phosphorylation and an increased rate of carbohydrate combustion after hypophysectomy. One cannot discard the evidence in favor of a substance of pituitary origin that inhibits the oxidation of glucose.

Himsworth, in a recent lecture (152), stated the following: "We can visualize the anterior pituitary gland as being concerned with adaptation to starvation, by retarding the utilization of sugar in the tissues, preventing the accelerating effect of insulin." In harmony with this view it would be of interest to assay single or pooled pituitary glands for antihexokinase activity in starved, fat-fed and carbohydrate fed rats. A negative result would be consistent with previous findings of Broh-Kahn & Mirsky (147), whereas fluctuations in association with the adaptation to a fat diet or to starvation would constitute presumptive evidence of the physiologic importance of an antihexokinase principle of pituitary origin.

Levine and his colleagues (153, 154) present a new and original concept of the mechanism of insulin action which implies that insulin may not necessarily exert its effect intracellularly. On the basis of experiments on the fall in blood galactose after insulin in the eviscerate animal, the Chicago investigators (154) believe that insulin acts on cell membranes in such a way that the transfer of both glucose and galactose across the membrane is facilitated. That there must be some degree of specificity of insulin action on hexoses, however, is indicated by their own report (153) which stresses the fact that the transfer of fructose from the extracellular fluid into the cell proceeds equally well in the presence or absence of insulin. This is not to be construed as a criticism of Levine's basic hypothesis, which, in the opinion of the reviewers, deserved further experimental testing.

In an excellent histochemical study of glycogen in adipose tissue, Fawcett (155) reminds us that the adipose tissue is by no means the metabolically inert region it was generally considered

to be in the days before Schoenheimer. He also stresses the role of insulin in the conversion of carbohydrate to fat and reviews much of the recent literature concerned with this important problem.

The pan-metabolic nature of insulin's action is further emphasized by the interesting report of Lotspeich (156). This investigator studied the blood concentration of the essential amino acids before and after a single injection of insulin in the normal dog. He found a remarkably constant pattern of the fall of individual acids after insulin, certain ones decreasing markedly, others to a smaller degree. Furthermore, he found a striking similarity between the pattern of fall in blood concentration on a molar basis and the pattern of the molar distribution of the acids in dog skeletal muscle protein hydrolysates. Finally (157), he made similar studies with purified anterior pituitary growth hormone and found essentially the same relationship between the fall in amino acid concentration of the blood and the representation of the individual acids in muscle protein. Although it is possible that an inhibition of deamination of amino acids could account for these results, it is more likely that they are indicative of protein synthesis.

*Insulin inactivation in the body.*—Having demonstrated that only vanishingly small amounts of insulin are recoverable from the urine of individuals given large amounts of this hormone (158), Mirsky and his colleagues assumed that insulin is probably destroyed in the animal body. They then described a heat labile, nondialyzable substance in homogenates of various tissues which is capable of destroying the physiological activity of insulin *in vitro* (141). The insulin-destroying activity of liver was found to be higher than that of any other tissue [see also (159)]. The reaction is potentiated by manganese and magnesium and is inhibited by copper, iodoacetate and iodosobenzoate. Moreover, the insulin-inactivating potency of liver homogenates prepared from starved (160) or fat-fed (161) rats is much lower than that of tissue obtained from carbohydrate fed rats. In a personal communication, Birnie (162) described similarly designed experiments that he has done with antidiuretic hormone of the posterior lobe of the pituitary. He finds a striking parallelism between his results and those reported by Mirsky *et al.* with insulin (141). Certain similarities between the insulin and pitressin molecules are known (163) and it is entirely possible that both substances may be inac-

tivated by the same system, although the starvation and diet experiments cited above constitute suggestive evidence of the specificity for insulin that the authors imply in naming their system "insulinase."

A systematic study of the mechanism of insulin inactivation in the body suggests many future experiments. One wonders, for example, whether or not a diabetic who is making moderate but inadequate amounts of insulin could be treated by means of the oral administration of an insulinase-inactivator as the mysathenic is treated with a cholinesterase inhibitor. It is possible that the potentiation of insulin action by sulfones, described by Macallum (164) is based on an inhibition of the destruction of insulin rather than on a directly synergistic effect between the sulfone and insulin. The fact that insulin sensitivity may persist for several days after the administered sulfone has been detoxified or eliminated lends support to this hypothesis.

#### THYROID

*Metabolism of the thyroid gland.*—The influence of the pituitary thyrotrophic hormone on the rate of iodine uptake by the human thyroid gland has been studied by Stanley & Astwood (165). The rate of uptake of tracer doses of radioiodine by the thyroids of normal human subjects and of normal subjects under treatment with thyroid was increased by thyrotrophic hormone for four or five days, the increase becoming apparent approximately 8 hr. after the pituitary hormone was given. This increase was not affected by the simultaneous administration of mercaptoimidazole, which inhibits the organic binding of iodide. This experiment suggests a direct effect of the pituitary on the capacity of the thyroid to collect iodine. If the increased rate of iodine uptake following thyrotrophic hormone administration was a result of iodine depletion caused by the release of large amounts of thyroid hormone, as suggested by Rawson (166), one would expect this effect to be altered by mercaptoimidazole.

In order to determine whether or not the colloid droplet formation in the rat thyroid epithelium known to follow thyrotrophic hormone administration is necessarily dependent on the pituitary, Dvoskin (167) studied droplet formation in hypophysectomized rats under various conditions. Although the typical response to cold or thiouracil did not occur in the absence of the pituitary,

droplet formation did follow toxic doses of various materials such as typhoid vaccine, histamine and others. Since agents which produced a response in the absence of the pituitary had to be given in toxic doses, the physiological significance of droplet formation in response to these stimuli might be questioned.

Fink & Fink (168), using radioiodine, were able to demonstrate the formation of appreciable amounts of monoiodotyrosine by rat thyroids and suggest that this compound may be involved in metabolism of iodine by the thyroid.

Continuing their studies of the inhibiting action of iodine on the thyroid, Wolff & Chaikoff (169) report that high plasma levels of iodine in the rat inhibit the formation of both diiodotyrosine and thyroxine in the thyroid. Their experiments did not, as they point out, reveal whether the inhibition of thyroxine formation was a direct effect on the conversion of diiodotyrosine to thyroxine or secondary to the resulting low levels of diiodotyrosine. The inhibition of thyroxine formation by high blood levels of iodine can not completely explain the action of iodine in hyperthyroid patients, according to Lesser and co-workers (170). They point out that in such patients iodine causes an accumulation of colloid in the thyroid follicles. They have been able to produce a similar accumulation of colloid in response to iodine in rats exposed to the cold for several weeks. These authors suggest that iodine may stimulate secretion of colloid into the lumen of the follicles by a mechanism related to its stimulating influence on salivation.

The antithyroid effect of thiocyanate is attributed by Baumann & Metzger (171) to its halogen-like properties. In their view, thiocyanate and halogens other than iodine act by competing with iodine for the mechanism by which the thyroid gland collects iodine. This hypothesis accounts for the prevention by large amounts of iodine of the antithyroid effect of these ions, but does not explain the finding of Vanderlaan & Vanderlaan (172) that small amounts of potassium thiocyanate administered to animals whose thyroid glands contain a large quantity of inorganic iodide causes an immediate discharge of all of it from the thyroid. Bromide does not behave in this way [see Astwood (173)].

The report of Van Middlesworth (174) that anoxic anoxia inhibits thyroid activity of rats as measured by the proportion of protein-bound iodine in the plasma, provides an *in vivo* illustration of the importance of oxidative enzymes in the synthesis of

thyroxine and diiodotyrosine from inorganic iodide, which had previously been demonstrated *in vitro* by Schachner, Franklin & Chaikoff (175).

*The metabolic fate and action of the thyroid hormone.*—Further evidence that the circulating thyroid hormone is actually thyroxine, loosely bound to protein, has been provided by Taurog & Chaikoff (176). They found that the iodine of normal plasma was almost completely extractable by butyl alcohol at room temperature, in contrast to thyroid gland iodine. Most of the butyl alcohol soluble iodine was not removed by a reagent which extracts diiodotyrosine and inorganic iodide, but not thyroxine, from this solvent. When crystalline thyroxine was added to plasma, it behaved like naturally occurring protein-bound iodine in several respects. Furthermore, when protein-bound iodine of rat plasma is labeled with  $I^{131}$  it follows thyroxine carrier quantitatively during crystallization or distribution between two immiscible solvents. Using an isotope dilution technique, Leblond & Gross (177) could show the release of thyroxine from an iodinated protein within the thyroid gland and its entry into the blood, thus supporting the same hypothesis by a physiological experiment.

In contrast to these reports, Salter & Johnston (178) found that thyroxine added to the serum of a patient with hyperthyroidism did not behave like the organically-bound iodine already present in such serum when the mixture was treated with acetone. In the same paper the results of studies on the nature of the hormone as it is found in peripheral tissues are described. The organic iodine of blood, lymph, and muscle was found to be distributed unevenly among the various protein fractions and in lymph and muscle as well as blood to fluctuate with variations in thyroid activity. When radioiodine was given to a rat in tracer doses it could be detected first in the inorganic iodine fraction from these tissues and later in protein-bound form. Similar results were obtained by Karandikar (179) when radioiodide or radioactive diiodotyrosine were given.

The suggestion was made by Issekutz *et al.* (180) that the circulating hormone must be incorporated in the enzyme system of the cell before becoming effective. They were unable to raise the  $Q_{O_2}$  of a suspension of red blood cells of normal birds by the addition of plasma from a thyroxine treated animal, although preparations from birds treated with thyroxine had an increased oxygen consumption *in vitro*. Another example of a failure of thyroxine to

exert an *in vitro* effect demonstrable when the hormone was given to the animal while still alive is presented by the experiments of Thibault (181, 182). She found that the inhibitory effect of epinephrine on isolated intestinal strips from rabbits was markedly prolonged when the animals had been treated with thyroxine. However, when thyroxine was added *in vitro* to the isolated strips from an untreated rabbit, this enhancing effect was not immediately apparent. Thibault further found that when thyroxine had been in contact with the isolated strip for an hour or more before testing, the prolongation of an epinephrine effect could be observed. Also, when such an incubated strip was extracted with Tyrode's solution, the resulting extract was active immediately on another strip. Apparently thyroxine must react with the tissue in some way before becoming active. It would be interesting to know whether or not a similar extract would have an effect on the  $Q_{O_2}$  of nucleated red blood cells *in vitro* if it could be suitably concentrated.

Radioactive iodine was incorporated into thyroxine chemically or biologically and used by Gross & Leblond (183) in a study of the distribution of the thyroid hormone in the rat. Large amounts of the labeled compound appeared in the liver and bile and eventually in the feces. Biological assay of the feces of lactating goats given thyroxine daily failed to account for more than 1 per cent of the injected material, according to a report of Monroe & Turner (184), although other workers have reported recovery of much larger proportions of administered thyroxine in the feces.

The liver is important in the breakdown of thyroxine as well as for its excretion. Sadhu & Truscott (185) believe that a disturbance of hepatic destruction of thyroid hormone is responsible for their finding that repeated large doses of vitamin A produce atrophy of the thyroid gland of rats and decreased concentration of iodine in liver and thyroid. In their view a piling up of thyroxine in this circumstance inhibits secretion of thyrotrophic hormone and secondarily leads to thyroid atrophy.

The effect of thyroxine on metabolic rate varies with different tissues studied *in vitro* by Brophy & McEachern (186). The  $Q_{O_2}$  of slices of kidney and muscle tissue from thyroxine treated rats was higher than control values, whereas the respiration of brain tissue was not affected by thyroxine treatment. The results with liver slices were not consistent,  $O_{O_2}$  values being higher than

normal in some preparations from thyroid treated rats and below normal in others. Low rates of oxygen consumption were raised above normal by the addition of succinate to the medium.

Whatever changes are produced in liver metabolism by the action of the thyroid hormone appear to involve an increased rate of phospholipid turnover as described by Flock *et al.* (187) and by Fraenkel-Conrat & Li (188), and a greater concentration of cytochrome-*c* and nucleic acid phosphorus (Drabkin, 108) with increased nucleic acid turnover (188). Drabkin observed that in spite of this effect on the liver composition of normal animals, when liver was regenerating after partial hepatectomy in thyroxine treated rats, the concentration of both cytochrome-*c* and nucleic acid phosphorus is reduced and the rate of liver regeneration is slower than that seen in untreated rats. In view of the findings of Rupp *et al.* (189) that, whereas large doses of thyroxine produce nitrogen loss, smaller doses in the physiological range were followed by nitrogen retention, it is possible that the effect of the hormone on regenerating liver might be reversed if smaller doses of thyroxine were given. The presence of the pituitary was necessary for any effect of thyroxine on nitrogen metabolism.

Although under certain circumstances there appears to be a synergism between the action of pituitary growth hormone and that of thyroxine on bone growth, Becks *et al.* (190) reported that when both hormones were given to hypophysectomized rats the predominating effect on the third metacarpal was that of the thyroid, producing epiphyseal closure with no evidence of synergism. The development of ossification centers in the rat [Noback *et al.* (191)] also appears to be controlled primarily by the thyroid with no modification of the effect by estrogen or androgen. The proceedings of a symposium on thyroid function held in 1947 under the auspices of the New York Academy of Sciences have been published (192).

#### PARATHYROID

Further evidence that the parathyroid hormone has a direct effect on bone metabolism has been provided by an experiment of Barnicot (193). Parathyroid glands from 10-day-old mice were attached to pieces of parietal bone from the same animal and transplanted to the cerebral hemisphere of a littermate. After 10 to 14 days the side of the bone nearer the parathyroid appeared

to be undergoing rapid resorption, whereas new bone deposition was occurring on the other side.

Several conflicting reports have appeared concerning the influence of the parathyroid on the renal excretion of phosphate. In agreement with many earlier reports, Handler *et al.* (194) and Cargill & Witham (195) have observed an increased excretion of phosphate in the urine after the administration of parathyroid extract. Handler and his collaborators, working with dogs, explained the increased phosphate excretion on the basis of an increased glomerular filtration rate which occurred soon after intravenous administration of parathyroid extract. They found no change in tubular reabsorption of phosphate. They believe that increased filtration rate is secondary to a rise in blood pressure caused by a pressor principle in parathyroid extract which may be identical with the calcium mobilizing hormone or an artifact created during the extraction procedure. Cargill & Witham, however found that intravenously injected parathyroid hormone had no effect on filtration rate in normal human subjects but did decrease phosphate reabsorption. However, when parathyroid hormone was given during or after glucose infusion the rate of phosphate reabsorption was increased.

Jahan & Pitts (196) reported that parathormone had no effect on reabsorption of phosphate by the kidney tubule of the dog when measurements were made 14 to 17 hr. after the second of two injections of the hormone. Since workers who have found an increased phosphate excretion following treatment with parathyroid hormone have observed the effect within a few hours after treatment, this observation does not necessarily conflict with reports of a parathyroid effect on phosphate reabsorption.

Stoerk & Silber (197) were unable to find an effect of parathyroid hormone on phosphate excretion of rats over a five-hour period unless the animals had been parathyroidectomized. Injection of 20 or more units of parathormone into parathyroidectomized rats increased the suppressed phosphate excretion to normal values, but doses up to 160 units had no further effect on phosphate excretion. This finding is in disagreement with observations of many other workers in the field.

Malcolm and co-workers (198) have reported the interesting observation that rats treated with thiourea and related compounds developed parathyroid hyperplasia and eventually osteitis fibrosa

with no renal disease. These rats also showed an enlargement of the pars intermedia of the pituitary. A relationship of parathyroid to plasma proteins of dogs was described by Malméjac *et al.* (199), who found an increase in  $\alpha$ -globulin and fibrinogen four to five days after parathyroidectomy.

## LITERATURE CITED

1. ANDERSON, E., *Ann. Rev. Physiol.*, **10**, 329-64 (1948)
2. ANDERSON, E., AND HAYMAKER, W., *J. Am. Women's Assoc.*, **3**, 402-6, 457-61 (1948)
3. HILLARP, N., *Acta Endocrinologica*, **2**, 11-23 (1949)
4. HARRIS, G. W., *J. Physiol. (London)*, **107**, 418-29 (1948)
5. BROLIN, S. E., *Acta Physiol. Scand.*, **14**, 233-44 (1947)
6. MARKEE, J. E., SAWYER, C. H., AND HOLLINSHEAD, W. H., *Recent Progress Hormone Research*, **2**, 117-31 (1948)
7. SAWYER, C. H., MARKEE, J. E., AND TOWNSEND, B. F., *Anat. Record*, **101**, 677-78 (1948)
8. NICKERSON, M., *Endocrinology*, **44**, 287-88 (1949)
9. SAWYER, C. H., MARKEE, J. E., AND EVERETT, J. W., *Proc. Soc. Exptl. Biol. Med.* (In press)
10. TEPPERMAN, J., AND BOGARDUS, J. S., *Endocrinology*, **43**, 448-89 (1948)
11. PASCHKIS, K. E., CANTAROW A., AND BOYLE, D., *Proc. Assoc. Study Internal Secretions*, **31**, 18 (1949)
12. PASCHKIS, K. E., CANTAROW, A., AND BOYLE, D., *Federation Proc.*, **8**, 123 (1949)
13. SEIFTER, J., EHRLICH, W. E., BEGANY, A. J., AND HUDYMA, G. M., *Federation Proc.*, **8**, 331-32 (1949)
14. WOLFSON, W. Q. (Personal communication, 1943)
15. HARFUDER, K., *Z. ges. exptl. Med.*, **42**, 1-14 (1924)
16. TUEKISCHER, E., AND WERTHEIMER, E., *Biochem. J.*, **42**, 603-9 (1948)
17. SOFFER, L. J., GABRILOVE, J. L., AND JAILER, J. W., *Proc. Soc. Exptl. Biol. Med.*, **71**, 117-19 (1949)
18. ELLINGER, F., *Radiology*, **51**, 394-99 (1948)
19. CHENG, C.-P., SAYERS, M. A., AND SAYERS, G., *Federation Proc.*, **8**, 24 (1949)
20. DEANE, H. W., SHAW, J. H., AND GREEP, R. O., *Endocrinology*, **43**, 133-53 (1948)
21. BERGNER, G. E., AND DEANE, H. W., *Endocrinology*, **43**, 240-60 (1948)
22. DEANE, H. W., AND GREEP, R. O., *Anat. Record*, **103**, 438 (1949)
23. D'ANGELO, S. A., *Federation Proc.*, **8**, 31 (1949)
24. GAARENSTROOM, J. H., AND DE JONGH, S. E., *Acta Endocrinologica*, **1**, 97-104 (1948)
25. MCQUILLAN, M. T., TRIKOJUS, V. M., CAMPBELL, A. D., AND TURNER, A. W., *Brit. J. Exptl. Path.*, **29**, 93-106 (1949)
26. MEITES, J., AND REED, J. O., *Proc. Soc. Exptl. Biol. Med.*, **70**, 513-16 (1949)
27. RINALDINI, L. M., *J. Endocrinol.*, **6**, 54-63 (1949)

28. FINERTY, J. C., AND BRISENO-CASTREJON, B., *Endocrinology*, **44**, 293-300 (1949)
29. GIROUD, A., AND MARTINET, M., *Compt. rend. soc. biol.*, **142**, 734-35 (1948)
30. SZEGO, C. M., AND WHITE, A., *Federation Proc.*, **8**, 153 (1949)
31. EDELMANN, A., *Brookhaven Conf. Rept.*, BNL-C-4, 72-77 (July 12-27, 1948)
32. MELLGREN, J., *Acta Path. Microbiol. Scand.*, **25**, 284-305 (1948)
33. GARDNER, W. U., *Cancer Research*, **8**, 397-411 (1948)
34. LONG, C. N. H., *Federation Proc.*, **6**, 461-71 (1947)
35. EVERETT, J. W., *Endocrinology*, **41**, 364-77 (1947)
36. TEPPERMAN, J., AND TEPPERMAN, H. M., *Endocrinology*, **41**, 187-95 (1947)
37. LEVIN, L., AND JAILER, J. W., *Endocrinology*, **43**, 154-66 (1948)
38. CLAESSON, L., AND HILLARP, N. A., *Acta Physiol. Scand.*, **14**, 102-19 (1947)
39. CLAESSON, L., DICZFALUSY, E., HILLARP, N. A., AND HÖGBERG, B., *Acta Physiol. Scand.*, **16**, 183-200 (1948)
40. ALDMAN, B., CLAESSON, L., HILLARP, N. A., AND ODERLAD, E., *Acta Endocrinologica*, **2**, 24-32 (1949)
41. GEMZELL, C. A., *Acta Endocrinologica*, **1** Suppl., 1-75 (1948)
42. VOGT, M., *Federation Proc.*, **8**, 341 (1949)
43. WILHELMI, A. E., FISHMAN, J. B., AND RUSSELL, J. A., *J. Biol. Chem.*, **176**, 735-45 (1948)
44. SMITH, E. L., BROWN, D. M., FISHMAN, J. B., AND WILHELMI, A. E., *J. Biol. Chem.*, **177**, 305-9 (1949)
45. BENNETT, L. L., LI, C. H., AND LAUNDRIE, B., *Proc. Soc. Exptl. Biol. Med.*, **68**, 94-95 (1948)
46. WHITNEY, J. E., BENNETT, L. L., LI, C. H., AND EVANS, H. M., *Endocrinology*, **43**, 237-39 (1949)
47. LI, C. H., SIMPSON, M. E., AND EVANS, H. M., *Endocrinology*, **44**, 71-75 (1949)
48. WHITNEY, J. E., BENNETT, L. L., LI, C. H., AND EVANS, H. M., *Proc. Soc. Exptl. Biol. Med.*, **69**, 118-19 (1948)
49. CHOW, B. F., AND GREEP, R. O., *Proc. Soc. Exptl. Biol. Med.*, **69**, 191-92 (1948)
50. BARTLETT, P. D., AND GAEBLER, O. H., *Endocrinology*, **43**, 329-35 (1948)
51. LI, C. H., GESCHWIND, I., AND EVANS, H. M., *Endocrinology*, **44**, 67-70 (1949)
52. KINSELL, L. W., MICHAELS, G. D., LI, C. H., AND LARSEN, W. E., *J. Clin. Endocrinol.*, **8**, 1013-36 (1948)
53. HURXTHAL, L. M., *Lahey Clinic Bull.*, **5**, 194-96 (1948)
54. BENNETT, L. L., GARCIA, J. F., AND LI, C. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 349-50 (1948)
55. SZEGO, C. M., AND WHITE, A., *Endocrinology*, **44**, 150-66 (1949)
56. PAYNE, R. W., *Federation Proc.*, **8**, 125-26 (1949)
57. ASLING, C. W., BECKS, H., SIMPSON, M. E., EVANS, H. M., AND LI, C. H., *Anat. Record*, **101**, 23-30 (1948)
58. COLLINS, D. A., BECKS, H., ASLING, C. W., SIMPSON, M. E., AND EVANS, H. M., *Ant. Record*, **101**, 13-16 (1948)

59. BAKER, B. L., AND INGLE, D. J., *Endocrinology*, **43**, 422-29 (1948)
60. WHITE, H. L., HEINBECKER, P., AND ROLF, D., *Am. J. Physiol.*, **156**, 67-78 (1949)
61. WHITE, H. L., HEINBECKER, P., AND ROLF, D., *Am. J. Physiol.*, **157**, 47-51 (1949)
62. RUSSELL, J. A., AND CAPIELLO, M., *Endocrinology*, **44**, 333-34 (1949)
63. LI, C. H., GESCHWIND, I., AND EVANS, H. M., *J. Biol. Chem.*, **177**, 91-95 (1949)
64. BARTLETT, P. D., *Federation Proc.*, **8**, 182 (1949)
65. KOCHAKIAN, C. D., AND STETTNER, C. E., *Am. J. Physiol.*, **155**, 262-64 (1948)
66. MATHIS, J. C., *Federation Proc.*, **8**, 226-27 (1949)
67. LI, C. H. *Growth*, **12**, Suppl., 47-60 (1948)
68. CONN, J. W., *Arch. Internal Med.*, **83**, 416-28 (1949)
69. PRUNTY, F. T. G., FORSHAM, P. H., AND THORN, G. W., *Clin. Sci.*, **7**, 109-20 (1948)
70. DEMPSEY, E. W., GREEP, R. O., AND DEANE, H. W., *Endocrinology*, **44**, 88-103 (1949)
71. NICHOLS, J., *J. Aviation Med.*, **19**, 171-78 (1948)
72. NICHOLS, J., *Arch. Path.*, **45**, 717-21 (1948)
73. NICHOLS, J., AND MILLER, A. T., JR., *Proc. Soc. Exptl. Biol. Med.*, **70**, 300-1 (1949)
74. ROBINSON, F. B., AND YOFFEY, J. M., *J. Anat.*, **83**, 81 (1949)
75. BOURNE, G. H., *J. Anat.*, **83**, 70 (1949)
76. JONES, I. C., *Proc. Soc. Exptl. Biol. Med.*, **69**, 120-21 (1948)
77. JONES, I. C., *Endocrinology*, **44**, 427-37 (1949)
78. LEATHEM, J. H., *Trans. N. Y. Acad. Sci.*, [2]2, 239-43 (1949)
79. FRANTZ, M. J., AND KIRSCHBAUM, A., *Proc. Soc. Exptl. Biol. Med.*, **69**, 357 (1948)
80. FRANTZ, M. J., AND KIRSCHBAUM, A., *Cancer Research*, **9**, 257-66 (1949)
81. KEYES, P. H., *Endocrinology*, **44**, 274-77 (1949)
82. COWIE, A. T., *J. Endocrinol.*, **6**, 94-98 (1949)
83. KATSH, S., GORDON, A. S., AND CHARIPPER, H. A., *Anat. Record*, **101**, 47 (1948)
84. SRERE, P. A., CHAIKOFF, I. L., AND GAUBEN, W. G., *J. Biol. Chem.*, **176**, 829-33 (1948)
85. CONN, J. W., AND VOGEL, W. C., *Proc. Assoc. Study Internal Secretions*, **31**, 16 (1949)
86. LLOYD, C. W., AND WILLIAMS, R. H., *Am. J. Med.*, **4**, 315-30 (1948)
87. HECHTER, O., *Federation Proc.*, **8**, 70 (1949)
88. KODAMA, S., *Chem. Abstracts*, **30**, 4907 (1936)
89. DUGAL, L. P., AND THÉRIEN, M., *Endocrinology*, **44**, 420-26 (1949)
90. HOCH-LIGETI, C., AND BOURNE, G. H., *Brit. J. Exptl. Path.*, **29**, 400-7 (1948)
91. MILLER, D. C., AND EVERETT, J. W., *Endocrinology*, **42**, 421-22 (1948)
92. DUMM, M. E., AND RALLI, E. P., *Endocrinology*, **43**, 283-92 (1948)

93. TEPPERMAN, J., ENGEL, F. L., AND LONG, C. N. H., *Endocrinology*, **32**, 403-9 (1943)
94. INGLE, D. J., GINTHER, G. B., AND NEZAMIS, J., *Endocrinology*, **32**, 410-14 (1943)
95. BENUA, R. S., AND HOWARD, E., *Endocrinology*, **36**, 170-77 (1945)
96. INGLE, D. J., *Endocrinology*, **37**, 7-14 (1945)
97. SELVE, H., *Ann. Internal Med.*, **29**, 403-15 (1948)
98. ENGEL, F. L., PENTZ, E. I., AND ENGEL, M. G., *J. Biol. Chem.*, **174**, 99-105 (1948)
99. ENGEL, F. L., SCHILLER, S., AND PENTZ, E. I., *Endocrinology*, **44**, 458-75 (1949)
100. BONDY, P. K., ENGEL, F. L., AND FARRAR, B., *Endocrinology*, **44**, 476-83 (1949)
101. ENGEL, F. L., *Proc. Assoc. Study Internal Secretions*, **31**, 17 (1949)
102. EVANS, G., *Endocrinology*, **29**, 737-39 (1941)
103. YOUNG, N. F., ABELS, J. C., AND HOMBURGER, F., *J. Clin. Invest.*, **27**, 760-65 (1948)
104. AWAPARA, J., MARVIN, H. N., AND WELLS, B. B., *Endocrinology*, **44**, 378-83 (1949)
105. NOBLE, R. L., AND TOBY, C. G., *J. Endocrinol.*, **5**, 303-13 (1948)
106. KLINE, D. L., *Am. J. Physiol.*, **154**, 87-93 (1948)
107. WHITE, A., HOBERMAN, H. D., AND SZEGO, C. M., *J. Biol. Chem.*, **174**, 1049-50 (1948)
108. DRABKIN, D. L., *Federation Proc.*, **8**, 195 (1949)
109. BAKER, B. L., INGLE, D. J., LI, C. H., AND EVANS, H. M., *Anat. Record*, **102**, 313-25 (1948)
110. LEVIN, L., *Federation Proc.*, **8**, 218-19 (1949)
111. LI, C. H., INGLE, D. J., EVANS, H. M., PRESTRUD, M. C., AND NEZAMIS, J. E., *Proc. Soc. Exptl. Biol. Med.*, **70**, 753-56 (1949)
112. BENNETT, L. L., SLESSOR, A., AND THORN, G. W., *Proc. Assoc. Study Internal Secretions*, **31**, 36 (1949)
113. BENNETT, L., GARCIA, J. F., AND LI, C. H., *Proc. Soc. Exptl. Biol. Med.*, **69**, 52-53 (1948)
114. BONDY, P. K., AND WILHELMI, A. E., *Federation Proc.*, **8**, 185-86 (1949)
115. FOLLEY, S. J., AND GREENBAUM, A. L., *Biochem. J.*, **43**, 581-84 (1948)
116. KOCHAKIAN, C. D., AND BARTLETT, M. N., *J. Biol. Chem.*, **176**, 243-47 (1948)
117. COWIE, A. T., FOLLEY, S. J., FRENCH, T. H., AND GREENBAUM, A. L., *J. Endocrinol.*, **6**, ii-iii (1949)
118. HENCH, P. S., *Proc. Staff Meetings Mayo Clinic*, **24**, 167-78 (1949)
119. HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H., AND POLLEY, H. F., *Proc. Staff Meetings Mayo Clinic*, **24**, 181-97 (1949)
120. HENCH, P. S., SLOCUMB, C. H., BARNES, A. R., SMITH, H. L., POLLEY, H. F., AND KENDALL, E. C., *Proc. Staff Meetings Mayo Clinic*, **24**, 277-97 (1949)
121. KENDALL, E. C., *Proc. Staff Meetings Mayo Clinic*, **24**, 298-301 (1949)
122. SELVE, H., SYLVESTER, O., HALL, L. E., AND LEBLOND, C. P., *J. Am. Med. Assoc.*, **124**, 201-7 (1944)

123. SELYE, H., *J. Clin. Endocrinol.*, **6**, 117-230 (1946)
124. OPSAHL, J. C., *Yale J. Biol. Med.*, **21**, 255-62 (1949)
125. HELLMAN, L., *Science*, **109**, 280-81 (1949)
126. LEWIS, L. A., AND PAGE, I. H., *Endocrinology*, **43**, 415-21 (1948)
127. INGLE, D. J., AND NEZAMIS, J. E., *Am. J. Physiol.*, **156**, 365-67 (1949)
128. INGLE, D. J., AND NEZAMIS, J. E., *Endocrinology*, **43**, 261-71 (1948)
129. LEGER, J., LEITH, W., AND ROSE, B., *Proc. Soc. Exptl. Biol. Med.*, **69**, 529-31 (1948)
130. TOBIAN, L., JR., AND STRAUSS, E., *Proc. Soc. Exptl. Biol. Med.*, **69**, 529-31 (1948)
131. INGLE, D. J., NEZAMIS, J. E., AND JEFFRIES, J. W., *Am. J. Physiol.*, **157**, 99-102 (1949)
132. DUREUIL, M., PROST, M., AND RATSIMANANGA, A., *Compt. rend. soc. biol.*, **142**, 723-26 (1948)
133. HOLTkamp, D. E., HILL, R. M., LONGWELL, B. B., RUTLEDGE, E. K., AND BUCHANAN, A. R., *Am. J. Physiol.*, **156**, 368-76 (1949)
134. COVIAN, M. R., *Proc. Assoc. Study Internal Secretions*, **31**, 40 (1949)
135. NICHOLS, J., *Proc. Soc. Exptl. Biol. Med.*, **69**, 29-31 (1948)
136. LAZAROW, A., *Physiol. Revs.*, **29**, 48-71 (1949)
137. BEST, C. H., HAIST, R. E., AND RIDOUT, J. H., *J. Physiol. (London)*, **97**, 107-19 (1939)
138. CONN, J. W., LOUIS, L. H., AND WHEELER, C. W., *J. Lab. Clin. Med.*, **33**, 651-61 (1948)
139. CONN, J. W., LOUIS, L. H., AND JOHNSTON, M. W., *J. Lab. Clin. Med.*, **34**, 255-69 (1949)
140. CONN, J. W., LOUIS, L. H., AND JOHNSTON, M. W., *Science*, **109**, 279-80 (1949)
141. MIRSKY, I. A., AND BROH-KAHN, R. H., *Arch. Biochem.*, **20**, 1-9 (1949)
142. BENNETT, L. L., AND LAUNDRIE, B., *Am. J. Physiol.*, **155**, 18-23 (1948)
143. BENNETT, L. L., *Am. J. Physiol.*, **155**, 24-27 (1948)
144. GAARENSTROOM, J. H., HUBLE, J., AND DE JONGH, S. E., *J. Endocrinol.*, **6**, 71-74 (1949)
145. REID, E., AND YOUNG, F. G., *Biochem. J.*, **42**, liv (1948)
146. STADIE, W. C., AND HAUGAARD, N., *J. Biol. Chem.*, **177**, 311-24 (1949)
147. BROH-KAHN, R. H., AND MIRSKY, I. A., *Science*, **106**, 148-49 (1948)
148. ZWILLING, E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 192 (1948)
149. KRAHL, M. E., AND PARK, C. R., *J. Biol. Chem.*, **174**, 939-46 (1948)
150. PERLMUTTER, M., AND GREEF, R. O., *J. Biol. Chem.*, **174**, 915-24 (1948)
151. REISS, M., BADRICK, F. E., AND HALKERSON, J. M., *J. Endocrinol.*, **6**, iv (1949)
152. HIMSWORTH, J., *Lancet*, **256**, 465-72 (1949)
153. LEVINE, R., LOUFE, S. D., AND WEISBERG, H. F., *Federation Proc.*, **8**, 95 (1949)
154. LEVINE, R., GOLDSTEIN, M., KLEIN, S., AND HUDDLESTON, B., *J. Biol. Chem.*, **179**, 985-86 (1949)
155. FAWCETT, D. W., *Endocrinology*, **42**, 454-67 (1948)
156. LOTSPEICH, W. D., *J. Biol. Chem.*, **179**, 175-80 (1949)

157. LOTSPEICH, W. D. (Personal communication, 1949)
158. MIRSKY, I. A., PODORE, C. J., WASHMAN, J., AND BROH-KAHN, R. H., *J. Clin. Invest.*, **27**, 515-19 (1948)
159. FRIEDMAN, A., WEISBERG, H. F., AND LEVINE, R., *Federation Proc.*, **8**, 52 (1949)
160. BROH-KAHN, R. H., AND MIRSKY, I. A., *Arch. Biochem.*, **20**, 10-14 (1949)
161. SIMKIN, B., BROH-KAHN, R. H., AND MIRSKY, I. A., *Federation Proc.*, **8**, 146 (1949)
162. BIRNIE, J. H. (Personal communication, 1949)
163. SEALOCK, R. R., AND VIGNEAUD, V. DU, *J. Pharmacol. Exptl. Therap.*, **54**, 433-47 (1935)
164. MACALLUM, A. B., *Can. J. Research*, **26**, 232-38 (1948)
165. STANLEY, M. M., AND ASTWOOD, E. B., *Endocrinology*, **44**, 49-60 (1949)
166. RAWSON, R. W., *Ann. N. Y. Acad. Sci.*, **50**, 491-607 (1949)
167. DVOSKIN, S., *Endocrinology*, **43**, 52-70 (1948)
168. FINK, K., AND FINK, R. M., *Science*, **108**, 358-59 (1948)
169. WOLFF, J., AND CHAIKOFF, I. L., *Endocrinology*, **43**, 174-79 (1948)
170. LESSER, A. J., WINZLER, R. J., AND MICHAELSON, J. B., *Proc. Soc. Exptl. Biol. Med.*, **70**, 571-73 (1949)
171. BAUMANN, E. J., AND METZGER, N., *Proc. Soc. Exptl. Biol. Med.*, **70**, 536-40 (1949)
172. VANDERLAAN, J. E., AND VANDERLAAN, W. P., *Endocrinology*, **40**, 403-16 (1947)
173. ASTWOOD, E. B., *Ann. N. Y. Acad. Sci.*, **50**, 419-43 (1949)
174. VAN MIDDLESWORTH, L., *Federation Proc.*, **8**, 158-59 (1949)
175. SCHACHNER, H., FRANKLIN, A. L., AND CHAIKOFF, I. L., *J. Biol. Chem.*, **151**, 191-99 (1943)
176. TAUROG, A., AND CHAIKOFF, I. L., *J. Biol. Chem.*, **176**, 639-56 (1948)
177. LEBLOND, C. P., AND GROSS, J., *J. Clin. Endocrinol.*, **9**, 149-57 (1949)
178. SALTER, W. T., AND JOHNSTON, M. W., *J. Clin. Endocrinol.*, **8**, 911-33 (1948)
179. KARANDIKAR, G., *Federation Proc.*, **8**, 84 (1949)
180. ISSEKUTZ, B., JR., GERGELY, J., AND HETÉNYI, G., JR., *Nature*, **163**, 363 (1949)
181. THIBAUT, O., *Compt. rend. soc. biol.*, **142**, 499-502 (1948)
182. THIBAUT, O., *Compt. rend. soc. biol.*, **142**, 502-4 (1948)
183. GROSS, J., AND LEBLOND, C. P., *Federation Proc.*, **8**, 62 (1949)
184. MONROE, R. A., AND TURNER, C. W., *Am. J. Physiol.*, **154**, 1-5 (1948)
185. SADHU, D. P., AND TRUSCOTT, B. L., *Endocrinology*, **43**, 120-23 (1948)
186. BROPHY, D., AND MCEACHERN, D., *Proc. Soc. Exptl. Biol. Med.*, **70**, 120-22 (1949)
187. FLOCK, E. V., BOLLMAN, J. L., AND BERKSON, J., *Am. J. Physiol.*, **155**, 402-8 (1948)
188. FRAENKEL-CONRAT, J., AND LI, C. H., *Endocrinology*, **44**, 487-91 (1949)
189. RUPP, J., PASCHKIS, K. E., AND CANTAROW, A., *Endocrinology*, **44**, 449-53 (1949)
190. BECK, H., ASLING, C. W., COLLINS, D. A., SIMPSON, M. E., LI, C. H., AND EVANS, H. M., *Anat. Record*, **101**, 17-22 (1948)

191. NOBACK, C. R., BARNETT, J. C., AND KUPPERMAN, H. S., *Anat. Record*, **103**, 49-67 (1949)
192. MEANS, J. H., ALBERT, A., ASTWOOD, E. B., CHAIKOFF, I. L., DEMPSEY, E. W., DEROBERTIS, E., GOLDSMITH, E. D., LEBLOND, C. P., MCGINTY, D. A., RAWSON, R. W., REINEKE, E. P., SALTER, W. T., AND TAUROG, A., *Ann. N. Y. Acad. Sci.*, **50**, 279-508 (1949)
193. BARNICOT, N. A., *J. Anat.*, **82**, 233-45 (1948)
194. HANDLER, P., DEMARIA, W. J. A., AND COHN, D. V., *Federation Proc.*, **8**, 204 (1949)
195. CARGILL, W. H., AND WITHAM, A. C., *Federation Proc.*, **8**, 21-22 (1949)
196. JAHAN, I., AND PITTS, R. F., *Am. J. Physiol.*, **155**, 42-49 (1948)
197. STOERK, H. C., AND SILBER, R. H., *Federation Proc.*, **8**, 371 (1949)
198. MALCOLM, J., GRIESBACH, W. E., BIELSCHOWSKY, F., AND HALL, W. E., *Brit. J. Exptl. Path.*, **30**, 17-23 (1949)
199. MALMÉJAC, J., CRUCK, S., NEVERRE, G., AND NAURIS, E., *Compt. rend. soc. biol.*, **142**, 505-7 (1948)
200. CORI, C. F., The Harvey Lectures, Series XLI, 253-72, 1945-46 (The Science Press, Lancaster, Pa.)

## REPRODUCTION<sup>1</sup>

By S. A. ASDELL

*Department of Animal Husbandry, Cornell University, Ithaca, New York*

We must begin, regretfully, by recording the death, on February 5, 1949, of F. H. A. Marshall, nearly 40 years after the appearance of the first edition of *The Physiology of Reproduction* (1). Dr. Marshall will be remembered for his pioneer work, for his clarity of thought and richness of exposition through the written word, and for his genial hospitality as the perfect host, always able to draw out the best in his guests. We are all, the writer especially, indebted to him for his leadership. This review is dedicated to his memory.

### THE MALE

*Artificial insemination.*—This year marks the end of the first decade of artificial insemination in dairy cattle as a practical venture, and it is fitting to give some idea of the progress which has been made. During the year about 2.5 million cows have been inseminated in the U.S.A. alone, and the enterprise which provides the semen and performs the inseminations is now a 12 million dollar industry employing more than 2,000 men and women full time. This large scale operation requires much organization and thought, so that fresh semen from bulls of a variety of breeds may be in the hands of inseminators when it is required. It is largely directed by cooperatives which derive their revenues from a levy of about six dollars for each cow enrolled. This provides for an initial insemination and two repeats if they prove necessary. In New York State, which has advanced, perhaps, furthest in organization, all the bulls are concentrated in a central barn; and semen is drawn from each bull about twice a week. A teaser cow is used, and the ejaculate is received in an artificial vagina, water jacketed, held beneath, or to one side of, the cow. A portion is then examined to see that it comes up to rigid standards of motility, concentration of sperm, and low percentage of abnormal forms. While this examination is in progress, the semen is gradually cooled to about 4° C., diluted with a buffered egg yolk-citrate

<sup>1</sup> This review covers the period from June 1, 1948 to June 1, 1949.

medium, and placed in vials for shipment. It is kept cool in transit by packing with it a toy balloon filled with ice. Shipment is made by many means of transit to the inseminators in the field. These men examine the samples for motility before they use them. The dairyman reports by telephone early each morning the number and breed of cows in heat so that the local technician can arrange his itinerary for the day. All inseminations are done with sterilized apparatus which is not used twice in one day, so that breeding a cow with semen from another breed and the transmission of disease can be avoided. Careful records are taken and transmitted to the Central Station where they are entered on International Business Machines (I.B.M.) punch cards so that continual checks upon the fertility of the bulls and the efficiency of operation can be made. Frequent schools for the training of inseminators are held at the Central Station.

This central organization has proved very effective, as it works in close conjunction with a research laboratory. In this way, modifications in management of bulls and of techniques may be tested by their effects upon the conception rate in hundreds of cows. In general, this runs at about 60 to 65 per cent cows in calf after 60 days, close to the rate found in natural service when the cows are brought to the bull for mating. The semen is usually one to two days old at the time of use. In some areas the semen is colored by nontoxic dyes, a distinctive color for each breed, before shipment in order to reduce the chance of error [Almquist (2)].

During the year, the First International Congress of Physiology and Pathology of Animal Reproduction and of Artificial Insemination was held at Milan, Italy, and the proceedings of this Congress have been published (3). Bonadonna (4) has drawn up specifications for the practice of artificial insemination and has reviewed its extent and the techniques used in Europe (5). Thibault reports the successful application of electro-ejaculation in the bull (6) and the ram (7). Swanson (8) has compared the effects of varying the composition of egg yolk-citrate buffer upon sperm motility, while Foote & Salisbury (9, 10), also Almquist *et al.* (11, 12), observed the effects of a variety of antibiotics upon semen. The results were variable. Salisbury & Bratton (13) found that the practical limit of dilution of bull semen for maximal fertility was 1:100 with a downward trend of 0.8 per cent for each decrease of a million sperm over the range, 15.3 to 2.36 million. Five to ten

million should be used as a rule. Addition of 300 mg. of sulphanilamide per 100 cc. semen allowed a dilution to 1:400, and the downward trend of fertility with fewer sperms was lessened. Schultze & Davis (14) found that 7  $\mu$ g. per cent of thyroxine increased the oxygen consumption of sperm if the concentration was above 800,000 per c.mm., but not at lower concentrations. Addition of thyroxine increased the fertility about 6 per cent (15). Prince & Almquist (16) have found that if the tubes containing semen are only partially filled, livability is decreased. This is due, in part, to the agitation caused in transport. Schultze *et al.* (17) found that, under field condition, fertility of semen declined 4.6 per cent with each day of storage, but that samples from individual bulls varied.

Turning to other species, Cheng & Casida (18) observed that, in the rabbit, maximal fertility was reached when 90,000 sperms were inseminated, but that partial fertility still existed at 16,000. Extreme dilution decreased the motility. Emmens & Swyer (19) saw a loss of motility in 2 to 3 hours at a dilution of 0.4 million per cc., but semen serum, secretions from vasectomized males, and a variety of colloidal solutions prevented this loss. This result is not universal in its application since Gilbreath & Davis (20) found that dilutions of turkey semen, even at 1:20 greatly reduced fertility, a result in line with experience in the fowl. Chang (21) tested the effect of heterologous seminal plasma upon the fertilizing capacity of rabbit spermatozoa. Human plasma had no ill effect, but bull plasma was harmful.

*Sperm metabolism.*—Ghosh *et al.* (22) could obtain no correlation between the metabolic activity of bull sperm after they were drawn and the fertilizing ability of the sample. Their result was based upon 702 inseminations. Barron *et al.* (23) report that soluble sulfhydryl (SH) groups are factors in the oxidation system of sea urchin sperm, while Rothschild (24) has evidence that cytochromes a,  $a_2$ , b, and c form the uptake system in this species. Vandermark *et al.* (25) show that excess of oxygen reduces the motility and livability of bull sperm by decreasing the conversion of sugar to lactic acid, an effect that can be prevented by the addition of catalase. Fructose continues to engage attention. Mann (26) has demonstrated that it is produced by the accessory glands, and that it is a measure of their functional ability. Fructolysis is low in a poor semen, and this sugar is metabolized by sperm both aerobically

and anaerobically (27). Citric acid, too, is a factor in metabolism. Humphrey & Mann (28) found it in seminal vesicle fluid, and, to a lesser extent, in prostatic fluid. It is metabolized at a slower rate than is fructose, to the metabolism of which it is not related. Semen from some species contains enzymes which can synthesize it; semen from others do not.

Pincus *et al.* (29) found that hyaluronidase inhibitors also inhibit the cell dispersing activity of this enzyme. When added to sperm suspension, they significantly reduce the number of ova fertilized in the ratio, sperm concentration to inhibitor concentration, a result which reopens the problem of hyaluronidase in relation to fertility.

Blandau & Oder (30) observed a great reduction in the number of sperm after insemination as they traverse the female tract of the rat. The number at the upper end of the oviduct is always low. Sykes *et al.* (31) sound a note of caution since testis biopsies have a harmful effect upon the bull's testis which may atrophy following the operation. Culp & Best (32) have studied the morphology of human sperm with the electron microscope.

*Testis activity.*—Schreiber (33) has studied testis stimulation by light in the frog. Imig *et al.* (34) find degeneration as a result of microwave irradiation in the rat. Infrared rays are not harmful unless the temperature rises to 40° C., when the same type of degeneration results. In the male starling, Burger (35) has observed that a rise in external temperature has some transient positive effect upon the testis during the nonbreeding season, but that the response is much larger when the birds are treated with additional light. Angulo (36) finds the thermoregulatory functions of the scrotum operative in a tropical rodent as well as in those inhabiting the temperate zone. According to Miller (37), a differential response to light and to gonadotrophes exists in birds of different species. This, he thinks, may be related to the migratory habit. Moreau *et al.* (38) report on cyclical changes in the testes of birds living near the equator. The resting period is during the long rainy and cool season. They regard the differences in the length of day and of temperature as too small to account for the changes observed. Reproduction in the tropics has been comparatively neglected; the assumption has been made that it is more or less continuous, but this is not so, and our theories will have to be modified as more data come in.

*Mating behavior.*—Grosch (39) reports that mating behavior in the male *Habrobracon* is dependent on the olfactory sense and that the stimulus is emitted by the abdomen of the female. Pauker (40) finds that the seminal vesicles and prostate are not involved in eliciting the mating reaction in hamsters, while Cheng & Casida (41) obtained increased sexual activity in male rabbits by injecting testosterone propionate; but sperm concentration and numbers were not affected.

#### THE FEMALE

A review of biological rhythms by Kleitman (42) contains material of interest. New studies include the common marine shrimp, by King (43); an oviparous lizard, by Miller (44); the mountain viscacha, by Pearson (45); pocket gopher, by Wood (46); an Indian vespertilionid bat (cyclical), by Gopalkrishna (47); the long tailed weasel, by Wright (48); balaenopterid whales, by Matthews (49); the bobcat, by Duke (50); the camel, by Tayes (51); the mule deer, by Chattin (52); and the chimpanzee, by Clark & Birch (53). The effect of high altitudes upon reproduction has been followed by Moore & Price (54) who report that 14,000 ft. elevation is without effect upon several rodents, while discontinuous exposure to 25,000 ft. is harmful to rats, according to Altland (55).

Factors affecting fertility and fecundity are of practical importance. One ingenious experiment is that by Calhoun (56), who found that distance from their food supply and the fights needed to reach it did not reduce the fertility of rats, but it did affect the number of young weaned. Seasonal factors affecting the lamb crop in merino ewes are reported by Morley (57). Inheritance is a factor in sows, according to Blunn Baker (58), while the whole subject of inheritance of fertility, as it affects dairy cattle, has been reviewed by Gilmore (59). Also, in cattle, Tanabe & Casida (60) have commented upon the high incidence of abnormal embryos, thus bringing another monotokous species in line with the polytokous ones.

*Ovulation factors.*—Farris (61) supplies further data on ovulation time in man, as determined by the rat test. Conception dates were from day 8 to 19, inclusive, with 60 per cent from day 11 to 13, inclusive. Newman (62) finds that electro-potentials are not accurate enough in man to serve as an index of ovulation time.

Cordiez (63) has reviewed the literature on ovulation time in the cow. Thibault *et al.* (64) have worked upon superovulation in the sheep, finding pregnant mares' serum effective in its production. The site of fertilization of the hen's egg is a problem which has attracted the attention of workers for years. Olsen & Neher (65) have reexamined the question and report that fertilization occurs after ovulation and before the egg reaches the magnum. They point out, however, that their technique does not rule out the possibility that, in exceptional cases, the egg may be fertilized in the ovary. Twining *et al.* (6) report that one service, in the ring-necked pheasant, fertilizes eggs for 21 days; further welcome evidence on this subject in birds. Rothchild & Fraps (67) give the interval between the release of the necessary hormone and ovulation in the fowl as 4 to 6 hr. Progesterone is ineffective in provoking ovulation after hypophysectomy; but, if the operation is performed four hours after the injection of this hormone, ovulation ensues normally (68), so that it is a factor in hypophyseal activation.

Brown *et al.* (69) have inhibited or delayed ovulation in man by giving diethylstilbestrol early in the cycle. Dutt & Casida (70) were able to lengthen cycles in the ewe by suppressing ovulation temporarily with progesterone.

Egg transfer, the analogue of artificial insemination, was the subject of a conference at San Antonio, Texas, this year, and the proceedings are to be published. The operation has been performed in cattle to the extent that implantation and development to 150 days followed. The hope is that superior cows can be superovulated and the eggs transferred to scrub cows for development, thus increasing the number of calves from the best cows. Meanwhile, Chang, (71, 72) has cooled fertilized rabbit ova and obtained development *in vitro* and after implantation into other rabbits. Cooling must be slow; 10° C. is the optimal temperature; storage is possible to four days; and the less the amount of cleavage at the time of cooling, the better. It may soon be possible to transport eggs, as well as semen.

*Neurohumoral factors.*—The writer has long believed that the role of the nervous system in reproduction is more important than is generally realized, so the following papers are of special interest to him. Kehl & Molina (73) found that gonadotrophes are ineffective in inducing ovulation in the rabbit when they are injected after novocaine, while Kasdon (74) had little success in inducing

ovulation with pictrotoxin, even when the rabbit was protected with phenobarbitol. Sawyer *et al.* (75), by injecting epinephrine, but not acetylcholine, directly into the anterior pituitary of rats, have caused the release of luteinizing hormone (LH), but dibenamine and atropine sulfate blocked this release. They concluded, therefore, that an adrenergic factor is responsible. Also (76), estrogen injected into pregnant rats on day four is followed by ovulation and cholesterol storage in the corpora lutea, and this, but not the LH effect, is blocked by benamine. Injected during proestrus (77), dibenamine retards or prevents ovulation. However, Nickerson (78) urges further experimental precautions before the final analysis of the relative importance of cholinergic and adrenergic factors is made.

In man, Bass (79) has reported that amenorrhoea occurred in 54 per cent of the women in a concentration camp, usually within four weeks of the beginning of internment, when nutritional factors could hardly have made their influence felt. Stroink (80) likewise reported that during the occupation of Holland amenorrhoea occurred in one-third of the young working women. No further cases appeared after the liberation unless the women lost weight. In half the cases, menstruation returned before nutrition improved. He concluded that the main cause was psychic, and he notes sudden shock and war weariness as factors. This is an aspect of reproduction which was given ample anecdotal treatment in the early literature, but it has been neglected of late. With the increase of knowledge of neurohumoral factors perhaps it should be regarded more seriously.

*Vascular patterns.*—Reynolds (61) has made an engineering study of the flow characteristics of arteries and, especially, of the slowing effect of the spiral arteries in the ovary of the rabbit. These studies have also been extended (82) to the human ovary, in which the patterns, helical spirals with diminishing diameters, are more complex than in the rabbit. The vascular pattern in the rat uterus as it is affected by estrogens and progesterone has been analyzed by Williams (83). The latter substance augments estrogen effects in the endometrium and lessens them in the myometrium. A technique using a radiopaque dye has been described by Gillespie & Reynolds (84) for measuring uterine circulation time in the intact primate.

*Menstruation.*—Kaiser (85) has failed to find any effect of

prostigmine in the rhesus monkey, and he concludes that menstruation does not depend upon hyperemia. In a review of the subject (86), he also rejects the spiral artery theory, partly on the basis of an experiment (87) which showed no growth of these arteries after massive doses of estrogen given to the rhesus monkey. Markee (88), in another review, concludes that all one can safely say at present is that menstruation follows local rapid endometrial regression, i.e., that rapid hormone withdrawal is necessary. In all, the year has been destructive to theories of menstruation; and we are back to our old position of ignorance.

Macht (89) has restudied the menstrual toxin, an early interest of his, and gives evidence for believing that it is a steroid. Weber *et al.* (90) have begun to open the problem of metestrous bleeding in the cow. Blood escapes both by diapedesis and by tissue destruction, though the latter is slight in comparison with that in the old world primates. Edwards & Duntley (91) bring up the subject of changes in vascularity of the skin in women and their relations to hormones. In their view, both the amount and the condition of the hemoglobin affect the picture.

*Pregnancy.*—A review of pregnancy diagnosis tests by Cowie (92) covers the subject adequately in man and other animals. Papers continue to appear on the male frog test which depends on the finding of spermatozoa in the urine of the frog. All the frogs and toads tried have proved useful. Marcenac & Vors (93) use intraocular grafts for reading the Friedman test, but it is a little slower than the orthodox method. Soule & Yanow (94) report that the Guterman pregnandiol test is 96.5 per cent accurate, while Behnken *et al.* (95) use the ovarian hyperemia test and find it 98.7 per cent accurate. The peak of gonadotrophin excretion is in the first trimester of pregnancy, and then it declines. Garrett (96) uses three injections of 1 mg. of estrone in oil in five days. If uterine bleeding fails to develop within 24 hr. of the third injection the woman is pregnant; 100 per cent accuracy is claimed for this test. Salvatore (97) has studied the cytology of uterine growth in the rat during pregnancy. Krehbiel (98) finds that cervicectomy and bypassing this organ does not prevent pregnancy in the rat. Brambell (99) has reviewed the subject of prenatal mortality in mammals. Nieburgs & Greenblatt (100) describe a smear test for diagnosing the fetal sex during pregnancy in man.

Histochemical studies of the secretion of mucus by the cervix

in man have been made by Atkinson *et al.* (101); secretion occurs at midcycle. Davids (102) reports on the activity of the oviduct during the menstrual cycle.

#### GENERAL ASPECTS

A paper which may lead to new ideas concerning reproduction and genetics in general is that by Monné (103) who describes the separation of structures resembling giant chromosomes from the cytoplasm when sea urchin eggs are treated with sodium azide.

*Fertilization.*—The maturation of anuran eggs under the influence of osmotic differentials has been studied by Tehou-Su (104) while the sensitization and activation of Nereis eggs has engaged the attention of Lefevre (105) who reports that the activator metabolite is produced within the egg. Krauss (106) has evidence that sea urchin fertilizin is a mucosaccharide with an action similar to that of hyaluronic acid since it produces a clot with mucin. This clot is equivalent to sperm agglutinate. Pequegnat (107) has obtained an inhibitor to the fertilization of Arbacia eggs from the amebocytes (blood cells) of Arbacia. This substance acts upon the fertilization membrane. Bielig & Medem (108) have reviewed the whole problem of substances involved in fertilization. Chang (109) reports that certain blood sera, but not others, are ovidical to fertilized rabbit eggs. Zlotnik (110) reports species differences in the behavior of the mitochondria and Golgi network in mammals during oögenesis. The respiratory metabolism of dividing rat eggs has been determined by Boell & Nicholas (111). It rises as the blastulae become more complex.

*Humoral control of sex differentiation.*—Coe (112) suggests that sex differentiation in the gastropod, *Crepidula plana*, depends upon the genetic constitution of the immature young. This determines to an extent their reaction to the environment, since not all of them develop as males when they are associated with a female. The problem in crustacea has been reopened by Reinhard (113) who points out that the bopyrid, *Stegophyxus hyptius*, larva is undifferentiated while it swims free. If it settles on a host crab it differentiates as a female, while in the food pouch of a female of its own species, it becomes a male. In *Rana sylvatica* Mintz (114) found that 1  $\mu$ g. of testosterone propionate per 1 l. of aquarium water caused the larvae to develop as males. In army ants, Schneirla (115) related nutrition or climate to sex determination,

since dry season conditions cause the queens to lay unfertilized eggs which develop as males. Eventually the queens become adapted to the conditions and lay fertilized eggs. Holyoke (116) transplanted embryonic rat gonads into the omentum of adults. Testes responded better than ovaries. A male host tended to masculinize the medulla and caused the production of an occasional ovotestis, while a female host tended to repress the medulla. The cortex was not affected by the sex of the host. Hart & Moody (117) have reviewed the effect of the age of the mammalian egg or sperm upon the secondary sex ratio. Their experimental work with rats confirms their view that, by delaying insemination, more males are produced. They were led to investigate this problem by the preponderance of males born after artificial insemination in man (118). No such report has come from the agricultural field, but perhaps the time factor is better under control.

*Steroid hormones.*—Techniques for hormone estimation rightly continue to engage much attention. Most work is directed toward estimation in the urine of man, a species which excretes more steroids than any other. The new edition of Fieser & Fieser (119) contains much useful information, especially on qualitative color tests. Articles by Pincus, by Pearlman, and by Dorfman, all in Pincus & Thimann (120) are also valuable. Dobriner *et al.* (121 to 123) have a series of papers on methods for neutral steroids; their chromatography and estimation by the use of infrared spectrometry. Fractionation of estrogens is discussed by Friedgood *et al.* (124); their fluorimetric determination by Jailer (125), and by Finkelstein (126). Biological assay of estrogens is reviewed by Rosenmund (127). Steroid sulfates are discussed by Klyne *et al.* (128); a rat test for testosterone by Wills *et al.* (129). Dorfman (130) has studied the response of the chick oviduct to methoxydusdehydro-doisyonic acid. It shows a skewed response, but not in sex-linked chicks. The colorimetric estimation of synthetic estrogens and their glucuronides in urine has been discussed by Malpress (131). Solubilities of natural steroids, especially in the presence of serum proteins, are given by Bischoff & Pilhorn (132). In this connection, Hooker & Forbes (133) point out that 90 per cent of the progesterone in blood plasma is free and the rest is bound or conjugated to protein.

*Progesterone.*—This steroid has been detected by Fraps *et al.* (134) in the blood plasma of ovulating hens, also (135) in that of

nonovulating hens and cocks, but it is absent in capons. Forbes & Hooker (136) show that protein-bound progesterone is inactive, and that, since pellets implanted in the spleen are inactive upon the endometrium, while bound progesterone increases in the blood, one hepatic function is to bind it. Administration of diethylstilbestrol to pregnant women does not increase the output of pregnandiol, according to Davis & Fugo (137). In cows, Pearlman & Cerceo (138) have isolated a variety of pregnandiols, etc., from bile, all unconjugated. Evidence accumulates that this is the main path for excretion of steroid hormones in this species. Kehl & Chambon (139) have worked out the relation between the dose of progesterone and the number of implantations in the rabbit. Harrison (140) has reviewed the development and fate of the corpus luteum in the vertebrates.

*Estrogens.*—The inactivation of estradiol by liver slices consumes oxygen, according to De Meio (141). Jailer (142) has found that not lack of vitamin B, but inanition, causes the liver to lose this function. Since the protein reserve of the liver decreases in inanition, one may speculate that protein binding may be involved to some extent. Biskind & Biskind (143) transplanted one rat ovary into the spleen. It retrogressed, but if the other ovary was removed corpora lutea developed and tended to produce luteoma. Mayer & Soumireu (144) find that autotransplantation of ovaries into the mesentery of the rabbit causes the tubular genitalia to retrogress.

In an ingenious experiment, Wang (145) joins half papillae of feathers from the back and saddle and studies the effect of estrogens upon the developing feathers. They retain their area specificity of response. Estrogens induce changes in the sexual skin of male baboons but not in male chimpanzees, according to Clark (146). Urist *et al.* (147) record species differences in the reaction of the skeleton to estrogens. In the view of Gillman & Gilbert (148), the physiological background of baboons used in experimental work modifies their response to estrogens.

East *et al.* (149), investigating the effect of the estrogen in subterranean clover upon guinea pigs and sheep, find that it affects castrated males, but not intact ones, and that androgens protect against it.

Knight (150) reviews the subject of theca-cell tumors of the ovary and provides further evidence that they secrete estrogens,

but not progesterone. Quin (151) records variation in the comb growth of cocks treated with different doses of stilbestrol which may give a clue to the action of the anterior pituitary under these conditions.

*Relaxin.*—Hisaw & Zarrow (152) report the absence of relaxin in the ovary of the sow during the follicular phase, but 2.5 to 5 guinea pig units are present per gm. of ovarian tissue in the lutein phase. In pregnancy, it increases to 10,000 G.P.U. per gm. It is also present in the blood and the placenta. Zarrow & Money (153) find that it is absorbed rapidly when it is injected and that it disappears rapidly from the blood. Work by Hall (154) provides evidence that progesterone given alone produces no wider relaxation of the mouse pelvis than does estrone. It inhibits relaxin and impairs the action of estrogens in 1.0 mg. daily dosage. This may explain why relaxation does not occur until late in pregnancy.

*Androgens, etc.*—Kimeldorf (155) finds that the excretion of 17-ketosteroids in the urine of male rabbits decreases by 41 per cent after castration, and that the experimental cryptorchid decreases its excretion to this level by 30 days, after which castration has no further effect. In the same species, de Koning *et al.* (156) could observe no differences in 17-ketosteroid excretion in normal and ovariectomized animals. Davis *et al.* (157) state that in male rabbits, androgens account for 3 per cent of the neutral ketones, while in the female the figure is 1 per cent. Schneider & Mason (158) have followed the metabolism of androsterone and etiocholan-3( $\alpha$ )-ol-17-one with rabbit liver slices. In the cockerel, Bernstorf (159) has reported partial hepatic inactivation of testosterone. Testosterone propionate does not increase the excretion of androgens or of 17-ketosteroids in the male cebus monkey, according to Henriquez *et al.* (160). Fecal androgen excretion in the cow occurs in the nonpregnant animal. In pregnancy, the amount does not increase until the last third of the period, and there is a large prepartum rise. Lactation does not affect its excretion rate. Jerseys excrete more than Holsteins or Guernseys [Turner (161)]. Casady *et al.* (162) find that feeding roughage increases it. According to them, the stage of pregnancy and lactation does not affect the level, while it increases after ovariectomy. In one ovariectomized cow, unilateral adrenalectomy increased the excretion.

Kar (163) reports the effects of androgen injection in the spotted munia, a common Indian bird, and Thyburg & Lyons

(164) give information upon its relation to the os penis of rats. Bern (165) finds that the threshold of testosterone for maintenance of the accessory organs of the male Dutch rabbit is of the order, 0.25 to 2.5 mg. daily. Estrogens maintain the tract at above the castrate level, and he suggests that this effect is due to the production of testoid metabolites from estrogens.

*Gonadotrophins.*—Li *et al.* (166) report the isolation of electrophoretically pure follicle-stimulating hormone (FSH). It proved to be follicle stimulating in hypophysectomized rat. Whitten (167) considers that gonadotrophes are similar to blood group specific substances in their destruction by certain enzymes. Products of estrogen inactivation by the liver do not inhibit the gonadotrophic functions of the pituitary, according to Jungch (168). Jones (169) shows that a pituitary hormone, probably LH, maintains the X-zone in the mouse adrenal. He believes that it is overridden by testosterone in the male and by an anterior pituitary-like (APL) substance from the conceptus or endometrium in the female. Kupperman *et al.* (170) obtain ovarian hyperemia only with LH or luteotrophic activity. Nalbandov & Baum (171) recommend the use of stilbestrol-inhibited males, preferably chickens, as test animals for gonadotrophic hormones.

*Lactation.*—Folley [in Pincus & Thimann (120)] has reviewed the present position in regard to mammary development and secretion. Trentin & Turner (172) find that the duct growth factor of the anterior pituitary is a protein, and they are unable to separate it from the alveolar growth factor. Estrogens produce end buds and alveoli. Under the conditions of their experiments, progesterone given alone caused only bud and duct growth, while the two together produced complete growth. Meites & Turner (173) show that estrogens increase the prolactin content of the pituitary, but excessive doses do not, though they do not cause a decline. In pregnancy, they believe, estrogens are held in check by progesterone. Removal of this inhibitor at parturition causes lactation. In a further paper (174), these authors discuss the factors which affect the prolactin content of the pituitary during lactation. Walker & Matthews (175) take a somewhat different view. Moderate doses of estrogens do not inhibit lactation in the castrate rat, but in higher doses they do, as they are toxic to the mother. Progesterone is without effect; estrogen with progesterone inhibits after 10 to 12 days, an effect due to new mammary growth. The

writer of this review is in sympathy with this interpretation. He does not believe that normal inhibition of lactation in pregnancy is an active one. Lactation does occur during pregnancy; it is a question of degree determined inversely by the amount of cellular growth. He believes that an "all or none" law operates upon the mammary cell. When it is growing and dividing under the influence of a stimulus, it cannot secrete. When the growth stimulus is removed, as at parturition, the cells secrete. Before they can do so, they have to get rid of some globulin, which appears, diluted with milk, as colostrum. Speert (176) has studied mammary development in the rhesus monkey. He finds mitoses throughout pregnancy, an important point in regard to the remarks made above.

*Nutrition.*—The past year has seen a period of "stock-taking" in regard to our knowledge of the relation between nutrition and reproduction. Russell (177) has a comprehensive review of the subject as it applies to rats and other laboratory animals; Reid (178) reviews it, principally in relation to domestic animals; and Asdell (179) to dairy cattle. In general, nutritional deficiencies are more harmful, and are less easily rectified, in the immature animal than they are in the adult. Small species of animals, with a higher rate of metabolism, appear to be more susceptible than do larger ones. Mirone *et al.* (180) find that in the mouse the nutritional requirements for reproduction are more stringent than are those for lactation. Goettsch (181) fed rats a diet in which the protein was from rice, beans and casein. The lower limit for efficient reproduction, and also for growth, was 16.7 per cent protein, and the limitation was probably due to a deficiency of methionine in the diet. Sherman *et al.* (182), in studies involving complete life cycles, obtained better reproduction in female rats on a 20 per cent protein level as contrasted to a 16 per cent level. In the same species, Maruyama & Phillips (183), using natural and purified diets, deduced that folic acid, L(+)-lysine, and DL-methionine are essential dietary factors for reproduction. Emerson *et al.* (184) analyzed the tissues of pregnant rats for several vitamins of the B group. These rats had been fed rations deemed satisfactory and unsatisfactory for reproduction, and the requirements in this species have been deduced from the results. Nelson & Evans (185), by inhibiting pyridoxine, obtained resorption of fetuses and stillbirths in rats. Vitamin A deficiency in the mother can cause failure of the male acces-

sory organs and of the vagina in the fetuses of rats [Wilson & Warkany (186)].

Gillman *et al.* (187), impressed by the prevalence of puerperal inversion of the uterus, and even its rupture, among the Chinese and the Bantu, have studied this question in rats and give evidence to show that its incidence increases when a low grade protein feed, maize, is fed. In a study of alloxan diabetes in rats, Sinden & Longwell (188) obtained evidence of reproductive failure which could be improved when insulin was given.

Romanoff & Romanoff (189) have made a comprehensive review of the avian egg, and Lesbouyries (190) has a new book on reproduction in domestic animals, especially useful for its description of the anatomy of the tract.

#### LITERATURE CITED

1. MARSHALL, F. H. A., *The Physiology of Reproduction*, 770 pp. (Longmans Green & Co., London, 1909, 1922)
2. ALMQUIST, J. O., *J. Dairy Sci.*, **29**, 815-20 (1946)
3. *Zootecnica e Veterinaria*, **3**, 82 pp. (June, 1948); Special Number, 103 pp. (June, 1948)
4. BONADONNA, T., *Attrezzatura e tecnica per la fecondazione artificiale dei bovini e degli equini* (Istituto L. Spallanzani, No. 5, Milan, 1948)
5. BONADONNA, T., *La fecondazione artificiale nel nord e nell' occidente europeo*, (Istituto L. Spallanzani, No. 6, Milan, 1948)
6. THIBAUT, C., LAPLAUD, M., AND ORTAVANT, R., *Compt. rend.*, **226**, 2006-8 (1948)
7. ORTAVANT, R., LAPLAUD, M., AND THIBAUT, C., *Compt. rend. acad. agr. France*, **34**, 733-36 (1948)
8. SWANSON, E. W., *J. Dairy Sci.*, **32**, 345-52 (1949)
9. FOOTE, R. H., AND SALISBURY, G. W., *J. Dairy Sci.*, **31**, 769-78 (1948)
10. FOOTE, R. H., AND SALISBURY, G. W., *J. Dairy Sci.*, **31**, 763-68 (1948)
11. ALMQUIST, J. O., GLANTZ, P. J., AND THORP, W. T. S., *J. Dairy Sci.*, **31**, 501-7 (1948)
12. ALMQUIST, J. O., GLANTZ, P. J., AND SHAFFER, H. E., *J. Dairy Sci.*, **32**, 185-90 (1949)
13. SALISBURY, G. W., AND BRATTON, R. W., *J. Dairy Sci.*, **31**, 817-22 (1948)
14. SCHULTZE, A. B., AND DAVIS, H. P., *J. Dairy Sci.*, **31**, 946-50 (1948)
15. SCHULTZE, A. B., AND DAVIS, H. P., *J. Dairy Sci.*, **32**, 322-26 (1949)
16. PRINCE, P. W., AND ALMQUIST, J. O., *J. Dairy Sci.*, **31**, 839-44 (1948)
17. SCHULTZE, A. B., DAVIS, H. P., BLUM, C. T., AND OLOUFA, M. M., *Nebraska Agr. Expt. Sta., Bull.*, 154 (1948)
18. CHENG, P., AND CASIDA, L. E., *Proc. Soc. Exptl. Biol. Med.*, **69**, 36-39 (1948)
19. EMMENS, C. W., AND SWYER, G. I. M., *J. Gen. Physiol.*, **32**, 121-38 (1948)
20. GILBREATH, J. C., AND DAVIS, G. T., *Poultry Sci.*, **28**, 406-10 (1949)

21. CHANG, M. C., *Proc. Soc. Exptl. Biol. Med.*, **70**, 32-36 (1949)
22. GHOSH, D., CASIDA, L. E., AND LARDY, H. A., *J. Animal Sci.*, **8**, 265-70 (1949)
23. BARRON, E. S. G., NELSON, L., AND ARDAO, M. I., *J. Gen. Physiol.*, **32**, 179-90 (1948)
24. LORD ROTHSCHILD, *J. Exptl. Biol.*, **25**, 15-21 (1948)
25. VANDERMARK, N. L., SALISBURY, G. W., AND BRATTON, R. W., *J. Dairy Sci.*, **32**, 353-60 (1949)
26. MANN, T., *J. Agr. Sci.*, **38**, 323-31 (1948)
27. MANN, T., AND LUTWAK-MANN, C., *Biochem. J.*, **43**, 266-70 (1948)
28. HUMPHREY, G. F., AND MANN, T., *Biochem. J.*, **44**, 97-105 (1949)
29. PINCUS, G., PIRIE, N. W., AND CHANG, M. C., *Arch. Biochem.*, **19**, 388-96 (1948)
30. BLANDAUI, R. J., AND ODER, D. L., *Anat. Record*, **103**, 93-110 (1949)
31. SYKES, J. F., WRENN, T. R., MOORE, L. A., UNDERWOOD, P. C., AND SULLIVAN, W. J., *J. Dairy Sci.*, **32**, 327-33 (1949)
32. CULP, O. S., AND BEST, J. W., *J. Urology*, **61**, 446-56 (1949)
33. SCHREIBER, V., *Compt. rend. soc. biol.*, **142**, 1055-57 (1948)
34. IMIG, C. J., THOMSON, J. D., AND HINES, H. M., *Proc. Soc. Exptl. Biol. Med.*, **69**, 382-86 (1948)
35. BURGER, J. W., *J. Exptl. Zool.*, **109**, 259-66 (1948)
36. ANGULO, J. J., *J. Mammalogy*, **30**, 54-57 (1949)
37. MILLER, A. H., *Science*, **109**, 546 (1949)
38. MOREAU, R. E., WILK, A. L., AND ROWAN, W., *Proc. Zool. Soc., London*, **117**, 345-64 (1947-48)
39. GROSCH, D. S., *J. Comp. Physiol. Psychol.*, **41**, 188-95 (1948)
40. PAUKER, R. S., *J. Comp. Physiol. Psychol.*, **41**, 252-57 (1948)
41. CHENG, P., AND CASIDA, L. E., *Endocrinology*, **44**, 38-48 (1949)
42. KLEITMAN, N., *Physiol. Revs.*, **29**, 1-30 (1949)
43. KING, J. E., *Biol. Bull.*, **94**, 244-62 (1948)
44. MILLER, M. R., *Univ. Calif. Pubs. Zool.*, **47**, 197-224, 225-46 (1948)
45. PEARSON, O. P., *Am. J. Anat.*, **84**, 143-74 (1949)
46. WOOD, J. E., *J. Mammalogy*, **30**, 36-44 (1949)
47. GOPALKRISHNA, A., *Proc. Indian Acad. Sci.*, **B26**, 219-31 (1947)
48. WRIGHT, P. L., *Am. Midland Naturalist*, **39**, 338-44 (1948)
49. MATTHEWS, L. H., *J. Anat.*, **82**, 207-32 (1948)
50. DUKE, K. L., *Anat. Record*, **103**, 111-32 (1949)
51. TAYES, M. A. F., *Vet. J.*, **104**, 179-86 (1948)
52. CHATTIN, J. E., *Calif. Fish Game*, **34**, 25-31 (1948)
53. CLARK, G., AND BIRCH, H. G., *Endocrinology*, **43**, 218-31 (1948)
54. MOORE, C. R., AND PRICE, D., *J. Exptl. Zool.*, **108**, 171-216 (1948)
55. ALTLAND, P. D., *J. Exptl. Zool.*, **110**, 1-17 (1949)
56. CALBOUN, J. B., *Science*, **109**, 333-35 (1949)
57. MORLEY, F. H. W., *Australian Vet. J.*, **24**, 106-11 (1948)
58. BLUNN, C. T., AND BAKER, M. L., *J. Animal Sci.*, **8**, 89-97 (1949)
59. GILMORE, L. O., *J. Dairy Sci.*, **32**, 71-91 (1949)
60. TANABE, T. Y., AND CASIDA, L. E., *J. Dairy Sci.*, **32**, 337-46 (1949)
61. FARRIS, E. J., *Am. J. Obstet. Gynecol.*, **56**, 346-52 (1948)

62. NEWMAN, H. F., *Am. J. Obstet. Gynecol.*, **56**, 901-6 (1948)
63. CORDIEZ, E., *Ann. Méd. Vét.*, **93**, 65-73 (1949)
64. THIBAUT, C., ORTAVANT, R., AND LAPLAUD, M., *Ann. endocrinol Paris*, **9**, 83-89 (1948)
65. OLSEN, M. W., AND NEHER, B. H., *J. Exptl. Zool.*, **109**, 355-66 (1948)
66. TWINING, H., HJERSMAN, H. A., AND MACGREGOR, W., *Calif. Fish Game*, **34**, 209-16 (1948)
67. ROTHCHILD, I., AND FRAPS, R. M., *Endocrinology*, **44**, 134-40 (1949)
68. ROTHCHILD, I., AND FRAPS, R. M., *Endocrinology*, **44**, 141-49 (1949)
69. BROWN, W. E., BRADBURY, J. T., AND JENNINGS, A. J., *J. Clin. Endocrinol.*, **8**, 453-60 (1948).
70. DUTT, R. H., AND CASIDA, L. E., *Endocrinology*, **43**, 208-17 (1948)
71. CHANG, M. C., *J. Gen. Physiol.*, **31**, 385-410 (1948)
72. CHANG, M. C., *Proc. Soc. Exptl. Biol. Med.*, **68**, 680-83 (1948)
73. KEHL, R., AND MOLINA, C., *Compt. rend. soc. biol.*, **142**, 1522-24 (1948)
74. KASDON, S. C., *Endocrinology*, **44**, 211-17 (1949)
75. SAWYER, C. H., MARKEE, J. E., AND TOWNSEND, B. F., *Endocrinology*, **44**, 18-37 (1949)
76. SAWYER, C. H., EVERETT, J. W., AND MARKEE, J. E., *Endocrinology*, **44**, 218-33 (1949)
77. EVERETT, J. W., SAWYER, C. H., AND MARKEE, J. E., *Endocrinology*, **44**, 234-50 (1949)
78. NICKERSON, M., *Endocrinology*, **44**, 287-88 (1949)
79. BASS, F., *Gynaecologia*, **123**, 211-19 (1947)
80. STROINK, J. A., *Gynaecologia*, **124**, 160-66 (1947)
81. REYNOLDS, S. R. M., *Acta Anat.*, **5**, 1-16 (1948)
82. DELSON, B., LUBIN, S., AND REYNOLDS, S. R. M., *Am. J. Obstet. Gynecol.*, **57**, 842-53 (1949)
83. WILLIAMS, M. F., *Am. J. Anat.*, **83**, 247-307 (1948)
84. GILLESPIE, E. C., AND REYNOLDS, S. R. M., *Proc. Soc. Exptl. Biol. Med.*, **70**, 721-24 (1949)
85. KAISER, I. H., *Am. J. Obstet. Gynecol.*, **56**, 664-72 (1948)
86. KAISER, I. H., *Am. J. Obstet. Gynecol.*, **56**, 1037-47 (1948)
87. KAISER, I. H., *Endocrinology*, **43**, 127-32 (1948)
88. MARKEE, J. E., *Bull. N. Y. Acad. Med.*, **24**, 253-68 (1948)
89. MACHT, D. I., *Am. J. Obstet. Gynecol.*, **57**, 251-60 (1949)
90. WEBER, A. F., MORGAN, B. B., AND McNUTT, S. H., *Am. J. Anat.*, **83**, 309-28 (1948)
91. EDWARDS, E. A., AND DUNTLEY, S. Q., *Am. J. Obstet. Gynecol.*, **57**, 510-19 (1949)
92. COWIE, A. T., *Pregnancy Diagnosis Tests: A Review*, 283 pp. (Joint Publ. No. 13, Commonwealth Bureau of Animal Breeding and Genetics Aberystwith, G. B., 1948)
93. MARCENAC, N., AND VORS, J., *Bull. acad. vét. France*, **21**, 98-103 (1948)
94. SOULE, S. D., AND YANOW, M., *Am. J. Obstet. Gynecol.*, **57**, 748-51 (1949)
95. BEHNKEN, E. W., LOYD, C. W., AND HUGHES, E. C., *Am. J. Obstet. Gynecol.*, **56**, 930-34 (1948)
96. GARRETT, S. S., *Am. J. Surg.*, **76**, 261-67 (1948)

97. SALVATORE, C. A., *Endocrinology*, **43**, 355-70 (1948)
98. KREHBIEL, R. H., *Anat. Record.*, **101**, 299-318 (1948)
99. BRAMBELL, F. W. R., *Biol. Revs. Cambridge Phil. Soc.*, **23**, 370-407 (1948)
100. NIEBURGS, H. E., AND GREENBLATT, R. B., *Am. J. Obstet. Gynecol.*, **57**, 356-63 (1949)
101. ATKINSON, W. B., SHETTLES, L. B., AND ENGLE, E. T., *Am. J. Obstet. Gynecol.*, **56**, 712-16 (1948)
102. DAVIDS, A. M., *Am. J. Obstet. Gynecol.*, **56**, 655-63 (1948)
103. MONNÉ, L., *Arkiv Zool.*, [A]**42**, (4), 11 (1949)
104. TEHOU-SU, *Acta Zool. Taiwanica*, **1**, 1-66 (1948)
105. LEFEVRE, P. G., *Biol. Bull.*, **95**, 333-45 (1948)
106. KRAUSS, M., *Biol. Bull.*, **96**, 74-89 (1949)
107. PEQUEGNAT, W. E., *Biol. Bull.*, **95**, 69-82 (1948)
108. BIELIG, H. J., AND MEDEM, F., *Experientia*, **5**, 11-30 (1949)
109. CHANG, M. C., *J. Gen. Physiol.*, **32**, 291-300 (1949)
110. ZLOTNIK, I., *Proc. Roy. Soc. Edinburgh*, **B63**, 200-12 (1948)
111. BOELL, E. J., AND NICHOLAS, J. S., *J. Exptl. Zool.*, **109**, 267-81 (1948)
112. COE, W. R., *J. Exptl. Zool.*, **108**, 155-69 (1948)
113. REINHARD, E. G., *Biol. Bull.*, **96**, 17-31 (1949)
114. MINTZ, B., *Proc. Soc. Exptl. Biol. Med.*, **69**, 358-61 (1948)
115. SCHNEIRLA, T. C., *Zoologica*, **33**, 89-112 (1948)
116. HOLYOKE, E. A., *Anat. Record*, **103**, 675-99 (1949)
117. HART, D., AND MOODY, J. D., *Ann. Surg.*, **129**, 550-71 (1949)
118. SEYMOUR, F. F., AND KOERNER, A., *J. Am. Med. Assoc.*, **116**, 2747 (1941)
119. FIESER, L. F., AND FIESER, M., *Natural Products Related to Phenanthrene*, 704 pp., (Reinhold Publishing Corp., New York, 1949)
120. PINCUS, G., AND THIMANN, K. V., *The Hormones, Physiology, Chemistry and Applications*, **1**, 886 pp. (Academic Press, Inc., New York, 1948)
121. DOBRINER, K., LIEBERMAN, S., AND RHOADS, C. P., *J. Biol. Chem.*, **172**, 241-61 (1948)
122. LIEBERMAN, S., DOBRINER, K., HILL, B. R., FIESER, L. F., AND RHOADS, C. P., *J. Biol. Chem.*, **172**, 263-95 (1948)
123. DOBRINER, K., LIEBERMAN, S., RHOADS, C. P., JONES, R. N., WILLIAMS, V. Z., AND BARNES, R. B., *J. Biol. Chem.*, **172**, 297-311 (1948)
124. FRIEDGOOD, H. B., GARST, J. B., AND HAAGEN-SMIT, A. J., *J. Biol. Chem.*, **174**, 523-54 (1948)
125. JAILER, J. W., *J. Clin. Endocrinol.*, **8**, 564-79 (1948)
126. FINKELSTEIN, M., *Proc. Soc. Exptl. Biol. Med.*, **69**, 181-84 (1948)
127. ROSENMUND, H., *Helv. Physiol. et Pharmacol. Acta*, **6**, 349-54, 355-70 (1948)
128. KLYNE, W., SCHACHTER, B., AND MARRIAN, G. F., *Biochem. J.*, **43**, 231-34 (1948)
129. WILLS, C. G., RAMPTON, S. E., AND PUGSLEY, L. I., *Endocrinology*, **44**, 251-58 (1949)
130. DORFMAN, R. D., *Endocrinology*, **43**, 232-36 (1948)
131. MALPRESS, F. H., *Biochem. J.*, **43**, 132-36 (1948)
132. BISCHOFF, F., AND PILHORN, H. R., *J. Biol. Chem.*, **174**, 663-82 (1948)
133. HOOKER, C. W., AND FORBES, T. R., *Endocrinology*, **44**, 61-66 (1949)
134. FRAPS, R. M., HOOKER, C. W., AND FORBES, T. R., *Science*, **108**, 86-87 (1948)

135. FRAPS, R. M., HOOKER, C. W., AND FORBES, T. R., *Science*, **109**, 493 (1949)
136. FORBES, T. R., AND HOOKER, C. W., *Proc. Soc. Exptl. Biol. Med.*, **70**, 682-85 (1949)
137. DAVIS, M. E., AND FUGO, N. W., *Proc. Soc. Exptl. Biol. Med.*, **69**, 436-38 (1948)
138. PEARLMAN, W. H., AND CERCEO, E., *J. Biol. Chem.*, **176**, 847-56 (1948)
139. KEHL, R., AND CHAMBON, Y., *Compt. rend. soc. biol.*, **142**, 674-76 (1948)
140. HARRISON, R. J., *Biol. Revs. Cambridge Phil. Soc.*, **23**, 296-331 (1948)
141. DE MEIO, R. H., RAKOFF, A. E., CANTAROW, A., AND PASCHKIS, K. E., *Endocrinology*, **43**, 97-104 (1948)
142. JAILER, J. W., *Endocrinology*, **43**, 78-82 (1948)
143. BISKIND, G. R., AND BISKIND, M. S., *Science*, **108**, 137-38 (1948)
144. MAYER, G., AND SOUMIREU, J., *Compt. rend. soc. biol.*, **142**, 964-67 (1948)
145. WANG, H., *J. Exptl. Zool.*, **109**, 451-501 (1948)
146. CLARK, G., *Yale J. Biol. and Med.*, **21**, 245-47 (1949)
147. URIST, M. R., BUDY, A. M., AND MCLEAN, F. C., *Proc. Soc. Exptl. Biol. Med.*, **68**, 324-26 (1948)
148. GILLMAN, J., AND GILBERT, C., *S. African J. Med. Sci.*, **13**, 121-44 (1948)
149. EAST, J., UNDERWOOD, E. J., AND BENNETTS, H. W., *Australian J. Exptl. Biol. Med. Sci.*, **27**, 105-13 (1949)
150. KNIGHT, W. R., *Am. J. Obstet. Gynecol.*, **56**, 311-24 (1948)
151. QUIN, J. I., *S. African Sci.*, **2**, 100-2 (1948)
152. HISAW, F. L., AND ZARROW, M. X., *Proc. Soc. Exptl. Biol. Med.*, **69**, 395-98 (1948)
153. ZARROW, M. X., AND MONEY, W. L., *J. Pharmacol. Exptl. Therap.*, **93**, 180-87 (1948)
154. HALL, K., *Quart. J. Exptl. Physiol.*, **35**, 65-75 (1949)
155. KIMELDORF, D. J., *Endocrinology*, **43**, 83-88 (1948)
156. DE KONING, J., KRICHESKY, B., AND GLASS, S. J., *Proc. Soc. Exptl. Biol. Med.*, **68**, 320-22 (1948)
157. DAVIS, C. T., SLATER, C. R., AND KRICHESKY, B., *Endocrinology*, **44**, 83-87 (1949)
158. SCHNEIDER, J. J., AND MASON, H. L., *J. Biol. Chem.*, **175**, 231-40 (1948)
159. BERNSTORF, E. C., *Proc. Soc. Exptl. Biol. Med.*, **69**, 447-48 (1948)
160. HENRIQUEZ, O. B., HENRIQUEZ, S. B., AND WENDEL, L., *Proc. Soc. Exptl. Biol. Med.*, **69**, 265-67 (1948)
161. TURNER, C. W., *J. Dairy Sci.*, **31**, 1032-40 (1948)
162. CASADY, R. B., COLE, H. H., AND HART, G. H., *J. Dairy Sci.*, **32**, 265-77 (1949)
163. KAR, A. B., *Proc. Zool. Soc. Bengal*, **1**, 81-89 (1948)
164. TRYBURG, W. G., AND LYONS, W. R., *Proc. Soc. Exptl. Biol. Med.*, **69**, 158-61 (1948)
165. BERN, H. A., *Am. J. Anat.*, **84**, 231-77 (1949)
166. LI, C. H., SIMPSON, M. E., AND EVANS, H. M., *Science*, **109**, 445-46 (1949)
167. WHITTEN, W. K., *Nature*, **163**, 534 (1949)
168. JUNGCH, E. C., *Proc. Soc. Exptl. Biol. Med.*, **69**, 527-29 (1948)
169. JONES, I. C., *Proc. Soc. Exptl. Biol. Med.*, **69**, 120-21 (1948)

170. KUPPERMAN, H. S., McSHAN, W. H., AND MEYER, R. K., *Endocrinology*, **43**, 275-82 (1948)
171. NALBANDOV, A. V., AND BAUM, G. T., *Endocrinology*, **43**, 371-79 (1948)
172. TRENTIN, J. J., AND TURNER, C. W., *Missouri Agr. Expt. Stas., Bull.*, 418 (1948)
173. MEITES, J., AND TURNER, C. W., *Missouri Agr. Expt. Stas., Bull.*, 415 (1948)
174. MEITES, J., AND TURNER, C. W., *Missouri Agr. Expt. Stas., Bull.*, 416 (1948)
175. WALKER, S. M., AND MATTHEWS, J. I., *Endocrinology*, **44**, 8-17 (1949)
176. SPEERT, H., *Carnegie Inst. Wash. Pub.*, **575**, 9-65 (1948)
177. RUSSELL, F. C., *Commonwealth Bur. Animal Nutrition, Tech. Commun.*, **16**, 98 (1948)
178. REID, J. T., *J. Am. Vet. Med. Assoc.*, **114**, 158-64, 242-50 (1949)
179. ASDELL, S. A., *J. Dairy Sci.*, **32**, 60-70 (1949)
180. MIRONE, L., PANZORELLA, F. P., AND CERECEDO, L. R., *Science*, **108**, 139-40 (1948)
181. GOETTSCHE, M., *Arch. Biochem.*, **21**, 289-300 (1949)
182. SHERMAN, H. C., CAMPBELL, H. L., AND RAGAN, M. S., *J. Nutrition*, **37**, 317-27 (1949)
183. MARUYAMA, G. M., AND PHILLIPS, P. H., *J. Nutrition*, **36**, 613-23 (1948)
184. EMERSON, G., WILLIAMS, E., WHEELER, E., SWANSON, P., SPIVEY, M., AND EPPRIGHT, M., *J. Nutrition*, **36**, 463-78 (1948)
185. NELSON, M. M., AND EVANS, H. M., *Proc. Soc. Exptl. Biol. Med.*, **68**, 274-76 (1948)
186. WILSON, J. G., AND WARKANY, J., *Am. J. Anat.*, **83**, 357-407 (1948)
187. GILLMAN, J., GILBERT, C., AND GILLMAN, T., *S. African J. Med. Sci.*, **12**, 151-60, 161-66 (1947)
188. SINDEN, J. A., AND LONGWELL, B. B., *Proc. Soc. Exptl. Biol. Med.*, **70**, 607-10 (1949)
189. ROMANOFF, A. L., AND ROMANOFF, A. J., *The Avian Egg*, 918 pp. (J. Wiley & Sons, New York, 1949)
190. LESBOUVRIES, G., *Reproduction des mammifères domestiques*, 712 pp. (Vigot Frères, Editeurs, Paris, 1949)

# AUTHOR INDEX

## A

- Aas, K., 453  
 Abbott, H. L., 109  
 Abel, M. S., 384  
 Abels, J. C., 514  
 Abelson, P. H., 11, 12  
 Abrams, M., 449  
 Abreu, B. E., 271  
 Acheson, G. H., 399  
 Ackroyd, J. B., 251  
 Adams, M. H., 307  
 Adams, W., 275, 334  
 Adams, W. S., 34  
 Addis, T., 390  
 Adelman, M. H., 356  
 Ades, H. W., 425  
 Adler, A., 474, 475  
 Adler, H. F., 192, 276, 277  
 Adler, P., 191  
 Adolph, E. F., 123, 126, 145, 160, 167, 290  
 Adolph, E. P., 379  
 Adolph, M. S., *see* Spiegel-Adolph, M.  
 Adrian, E. D., 399, 469, 473, 478, 479, 481  
 Ahrens, E. H., Jr., 166  
 Aitken, C. J., 359  
 Ajo, A., 498  
 Ajuriaguerra, J. de, 461  
 Alajouanine, J., 434  
 Albert, A., 528  
 Albert, R. E., 139, 451  
 Albright, F., 108, 110  
 Albrink, W. S., 399  
 Alburn, H. E., 253  
 Aldman, B., 508  
 Aldrich, R. A., 76  
 Aleksandrov, V. Y., 11  
 Allala, A., 436  
 Alexander, B., 241, 243, 244, 250  
 Alexander, F., 453  
 Alexander, I. E., 167  
 Alexander, J. D., 163  
 Alford, W. C., 192  
 Allen, J. G., 33, 253  
 Allen, R. P., 171  
 Allen, R. S., 206  
 Allen, T. H., 325  
 Allen, W. F., 430, 447, 473, 480, 481  
 Allison, A. C., 424  
 Allison, J. B., 328  
 Almquist, J. O., 538, 539  
 Almy, T. P., 225  
 Alper, T., 31  
 Alphonse, P., 164  
 Alquist, R. P., 345  
 Alston, E. J., 330, 455  
 Altamirano, M., 456  
 Althausen, T. L., 226, 227  
 Altland, P. D., 187, 275, 541  
 Altman, K. I., 76  
 Altschul, A. M., 304  
 Altschule, M. D., 269, 328  
 Alving, A. S., 334  
 Alwall, N., 391  
 Amado, D., 101  
 Amador, L. V., 432  
 Amassian, V. E., 475  
 Ambache, N., 225, 353  
 Ament, R., 183  
 Ames, A., 125  
 Amprino, R., 101  
 Anderson, A., 214  
 Anderson, B. G., 247  
 Anderson, C. E., 227  
 Anderson, E., 503  
 Anderson, G. A., 158  
 Anderson, J. T., 293  
 Andréén, N., 11  
 Andrews, H. L., 29  
 Andronis, A., 352  
 Anfinsen, C. B., 73, 74, 80  
 Angel, R., 225  
 Angell, E., 330, 455  
 Angulo, J. J., 540  
 Annegers, J. H., 219, 226  
 Anrep, G. V., 358  
 Anslow, W. P., Jr., 158, 159, 161, 162, 163, 372  
 Antia, F., 215  
 Apperly, F. L., 278, 317  
 Archdeacon, J. W., 161, 206, 449  
 Archer, S., 229  
 Archibald, R. M., 380  
 Ardao, M. I., 539  
 Arditi, J., 191  
 Arends, R. L., 277  
 Arieff, A. J., 436, 451  
 Arkin, A., 39  
 Armstrong, W. D., 76, 105, 106, 111  
 Arnott, W. M., 315  
 Arnould, P., 378  
 Arshavski, I. A., 179  
 Arvy, L., 256  
 Ascenzi, A., 101, 102  
 Aschan, G. K., 192  
 Aschoff, J., 319, 320  
 Asdell, S. A., 550  
 Ashby, W. R., 422  
 Ashler, F. M., 38  
 Ashman, R., 361, 363  
 Ashworth, M. A., 322  
 Asling, C. W., 86, 87, 101, 108, 109, 509, 528  
 Asmussen, E., 136, 182, 276  
 Assali, N. S., 388  
 Aste-Salazar, H., 187, 275  
 Aström, A., 330  
 Astrom, K. E., 437  
 Astrup, P., 252, 253  
 Astrup, T., 255  
 Astwood, E. B., 524, 525, 528  
 Atkinson, W. B., 545  
 Atkinson, W. J., 451  
 Attardo, F. P., 451  
 Attyuh, A. M., 277  
 Aub, J. C., 88, 112  
 Auerbach, C., 48  
 Auerbach, M. E., 330, 455  
 Auerbach, O., 251  
 Auerswald, W., 499  
 Ausherman, H. M., 191, 277  
 Austin, G. M., 271, 321, 459  
 Austin, M. L., 65  
 Autio, L., 315  
 Avera, J. W., 192, 316, 323, 331, 459  
 Avery Jones, F., 385  
 Aviado, D. M., 182, 183, 193, 266, 267, 353, 458  
 Awapara, J., 73, 79, 514  
 Axelrod, B., 75  
 Axelrod, D. J., 105  
 Axelrod, H. E., 108  
 Axelrod, J., 150  
 Axtrup, S., 246  
 Ayer, J. L., 371

## B

- Baarsma, P. R., 179  
 Babkin, B. P., 210  
 Bach, L. M. N., 435  
 Bach, W., 192  
 Bacq, Z. M., 384  
 Bader, M. E., 130, 131, 318, 319  
 Bader, R. A., 126, 157  
 Bader, R. E., 124  
 Badrick, F. E., 522  
 Baer, H., 171  
 Baez, S., 329, 382, 387  
 Bagdy, D., 254  
 Baggenstoss, A. H., 221  
 Baidens, A., 37  
 Bailey, P., 428, 474  
 Baker, B. L., 108, 109, 111, 509, 515  
 Baker, C., 351  
 Baker, H. D., 499  
 Baker, K. E., 499  
 Baker, M. L., 541  
 Baker, R. F., 20  
 Bakos, A. C. P., 181  
 Bakst, H., 358  
 Balaban, M., 349  
 Baldwin, E. D., 185  
 Baldwin, E. deF., 192, 330, 352  
 Bale, W. F., 77  
 Bales, P. D., 450  
 Ball, S., 486, 487  
 Ballin, H. M., 431, 432  
 Bancroft, R. W., 187  
 Banfield, W. G., 272  
 Bang, F. B., 19, 20  
 Banister, J., 192, 270  
 Banner, R. L., 192  
 Barach, A. L., 179, 189, 275  
 Barach, B., 275  
 Barclay, A. E., 227, 373, 374, 378, 379, 382, 384  
 Barclay, J. A., 373  
 Barcroft, H., 316, 330, 352, 453  
 Barcroft, J., 267, 322, 379  
 Bard, P., 430, 446  
 Bardwell, K., 279  
 Bare, J. K., 471, 472  
 Barga, J. A., 222, 224, 453  
 Barger, J. D., 103  
 Barillet, F., 29  
 Barker, E. S., 183, 193, 266, 267  
 Barker, H. G., 151, 273  
 Barker, N. W., 244, 245, 253, 255, 386  
 Barker, S. B., 293, 295  
 Barnard, R., 252  
 Barnes, A. R., 192, 359, 516, 517  
 Barnes, D. W. H., 326  
 Barnes, E. C., 29  
 Barnes, J., 461  
 Barnes, J. R., 295  
 Barnes, R. B., 546  
 Barnes, R. H., 81, 295  
 Barnett, H. L., 151, 152, 369, 370  
 Barnett, J. C., 528  
 Barnhart, M., 435  
 Barnicot, N. A., 528  
 Barnum, C. P., 105  
 Baronofsky, I. D., 216  
 Barr, M. L., 14  
 Barratt, R. W., 49  
 Barreda, P. de la, *see de la Barreda, P.*  
 Barrett, M. J., 120, 289, 296  
 Barrett, R., 85  
 Barrett, W., 222  
 Barron, D. H., 270, 383, 425, 448  
 Barron, E. S. G., 30, 31, 300, 304, 539  
 Barry, G. T., 72, 83  
 Barsoum, G. S., 358  
 Bartels, C. C., 334  
 Barthe, C., 256  
 Bartlett, G. R., 300, 304  
 Bartlett, M. N., 516  
 Bartlett, P. D., 509  
 Barton, G. D., 278  
 Bass, D. E., 124, 157  
 Bass, F., 543  
 Bassett, R. C., 316, 331  
 Bate, E. W., 352  
 Batiuchock, W., 357  
 Batten, W., 390  
 Battista, A. F., 122, 432  
 Battro, A., 192, 346  
 Baud, C. A., 101  
 Baudouin, A., 192  
 Bauer, A. J., 30  
 Bauer, J., 384  
 Bauer, W. H., 106, 111  
 Baum, G. T., 549  
 Baumann, C. A., 81  
 Baumann, E. J., 525  
 Baumberger, P., 279  
 Baumgardt, E., 498  
 Baxter, J. H., 384  
 Bays, R. P., 243  
 Bazett, H. C., 121, 128, 277, 314, 319, 350  
 Beach, F. A., 112  
 Beadle, G. W., 61, 82  
 Beakey, J. F., 192  
 Beale, G. H., 59, 66  
 Beams, H. W., 19  
 Bean, D. M., 192  
 Bean, J. W., 189, 225  
 Beattie, J., 294  
 Beatty, C. H., 328, 329  
 Beauvallet, M., 449  
 Bech, P. F., *see Fönss-Bech, P.*  
 Beck, C. S., 191, 357  
 Beck, E., 428  
 Beck, H., 528  
 Beck, L. H., 477  
 Beck, R. D., 108  
 Beckett, S., 430, 431  
 Becks, H., 86, 87, 101, 107, 108, 109, 509  
 Beebe-Center, J. G., 470  
 Beecher, H. K., 302  
 Beer, B. V. A. L., *see Low-Beer, B. V. A.*  
 Beers, N. R., 28  
 Begany, A. J., 253, 505  
 Behnke, A. R., 180, 266, 273  
 Behnken, E. W., 544  
 Behrmann, V. G., 192, 278, 279  
 Bein, H. J., 330  
 Bekaert, J., 459  
 Belding, H. S., 125, 130, 319  
 Bell, G. H., 107, 324  
 Bell, R., 187  
 Bell, R. M., 326  
 Bellet, F. M., *see Martin-Bellet, F.*  
 Bello, C. T., 334  
 Beloff, A., 73, 74, 80  
 Belt, M., 79  
 Bembower, W. C., 180  
 Bender, M. B., 449  
 Benditt, E. P., 295  
 Benesch, R., 103  
 Benjamin, H. R., 171  
 Benjamin, J. M., Jr., 312, 352  
 Bennett, A., 350, 390  
 Bennett, I. L., 246  
 Bennett, L. L., 86, 508, 509, 516, 521  
 Bennett, W. D., 357  
 Bennetts, H. W., 547  
 Benoit, J., 109, 110, 111  
 Benotti, J., 221

- Benoy, M. P., 299  
 Benson, A. A., 77  
 Bentley, F. H., 227  
 Benua, R. S., 513  
 Benzer, P., 104  
 Benzinger, T. H., 119, 120  
 Bercu, B. H., 164  
 Berg, M., 216  
 Berg, R. M., 192  
 Berg, W. E., 183, 293  
 Bergamo, G., 453  
 Berger, A. R., 128  
 Berger, E. Y., 151, 163  
 Bergman, H. C., 383  
 Bergner, G. E., 506, 509  
 510  
 Berk, L., 268  
 Berkeley, E., 16  
 Berkson, J., 528  
 Berle, B., 225  
 Berliner, R. W., 371, 372  
 Bern, H. A., 549  
 Bernfeld, P., 220  
 Bernius, B., 246  
 Bernstorff, E. C., 548  
 Berry, W. T. C., 313  
 Berseus, S., 277, 349  
 Bertram, E. G., 14  
 Bessis, M., 20, 250, 252  
 Best, C. H., 520  
 Best, J. W., 540  
 Bevelander, G., 104  
 Beveridge, J. B., 313  
 Bevers, C. A., 104  
 Beyne, J., 192  
 Bidoggia, H., 192, 346  
 Bielg, H. J., 545  
 Bielschowsky, F., 529  
 Bienvenu, B., 160  
 Bigelow, R. R., 209  
 Biggs, R., 245, 254  
 Billingham, R. E., 67  
 Bills, C. E., 108  
 Bilski, R., 211  
 Binet, L., 184, 191, 192,  
 277, 315, 316, 329, 332,  
 455, 458  
 Bing, R. J., 272, 277, 348,  
 359, 377, 380  
 Bingham, W. G., 425  
 Biörck, G., 192  
 Birch, H. G., 541  
 Birchall, R., 334  
 Bircher, R., 459  
 Bird, R. M., 301, 302  
 Birmingham, M. K., 302  
 Birnie, J. H., 158, 523  
 Birukow, G., 499  
 Bischoff, F., 546  
 Bishop, G. H., 434  
 Biskind, G. R., 547  
 Biskind, M. S., 547  
 Bixby, E. W., 124, 167,  
 327, 329  
 Bizard, G., 322  
 Bjerver, K., 192  
 Bjurstedt, H., 190  
 Black, A., 294  
 Black, D. A. K., 333, 383,  
 385, 459  
 Black, H., 265  
 Blackburn, C. M., 212,  
 213  
 Blair, H. A., 399, 404  
 Blake, W. D., 161, 164,  
 323  
 Blakemore, A. N., 255  
 Blakeslee, A. F., 470  
 Bland, J. H., 380  
 Blandau, R. J., 540  
 Blegen, E., 453  
 Blewett, M., 79  
 Blickenstaff, D., 212, 228  
 Blinn, K. A., 192  
 Bliss, A. F., 486, 487, 488,  
 489  
 Bliss, H. A., 229, 312  
 Bloch, K., 75  
 Block, M. H., 33, 253  
 Block, S., 214  
 Blockley, W. V., 125  
 Blood, D. W., 246  
 Blood, F. R., 189, 191,  
 276  
 Bloom, F., 253  
 Bloomfield, A. L., 229  
 Blott, P. A., 380  
 Blount, H. C., Jr., 40  
 Bloxsom, A., 391  
 Blum, C. T., 539  
 Blum, M., 474  
 Blumenthal, G., 31  
 Blumstein, G. I., 192  
 Blunn, C. T., 541  
 Bluntschli, H. J., 389  
 Boche, R. D., 193  
 Bodansky, O., 104, 269  
 Boell, E. J., 545  
 Boer, J. de, 331  
 Bogardus, J. S., 504  
 Bohnhoff, M., 60  
 Bøje, O., 132  
 Boldrey, E., 474  
 Bollman, J. L., 221, 244,  
 247, 324, 528  
 Bolomey, A. A., 158, 334,  
 350, 388  
 Bölönyi, F., 454  
 Bonadonna, T., 538  
 Bonard, E. C., 454  
 Bondy, P. K., 513, 514,  
 516  
 Bonet-Maury, P., 30  
 Bonham, K., 32, 33  
 Bonin, G. von, *see von*  
 Bonin, G.  
 Bonner, D., 50, 53, 54  
 Bonner, D. M., 73, 78  
 Bonner, J., 10  
 Bonnet, V., 103  
 Bonnevie, K., 15  
 Bonsdorff, E., 187, 330  
 Bonvallet, M., 449, 451  
 Booker, W. M., 193, 376  
 Boone, A. W., 357  
 Boone, B. R., 346  
 Boothby, W. M., 183  
 Borden, C., 184, 348  
 Borek, E., 83  
 Borge, A. F., 425  
 Borison, H. L., 181, 228,  
 435, 450  
 Bornstein, F. P., 251  
 Börnstein, W. S., 470, 474,  
 475  
 Borsodi, L., 252  
 Borsook, H., 72, 75, 77  
 Borst, J. G. G., 163  
 Boshes, B., 451  
 Boss, W. R., 158  
 Bosshardt, D. K., 81, 295  
 Botelho, S. Y., 124, 278,  
 316  
 Botterell, E. H., 425  
 Bouckaert, J. J., 320, 459  
 Bouma, P. J., 485  
 Bouman, M. A., 485, 499  
 Bourne, G. H., 104, 107,  
 510, 513  
 Bourret, J., 33  
 Bouvet, M., 428  
 Bovet, D., 461  
 Bovet-Nitti, F., 461  
 Bowen, W. J., 192, 193,  
 275  
 Bowers, H. N., 424  
 Bowers, J. Z., 29  
 Boy, G., 276  
 Boyarsky, S., 215  
 Boyd, E. J., 246  
 Boyd, G. E., 30  
 Boyd, G. H., 328  
 Boyd, L. J., 214  
 Boyd, M. J., 73  
 Boyden, E. A., 192  
 Boyle, D., 505  
 Boyle, P. J., 147  
 Boynton, R. E., 313, 332  
 Bozler, E., 459  
 Braasch, W. F., 386

- Brachet, J., 11, 14, 15, 19  
 Bradbury, J. T., 542  
 Bradley, S. E., 161, 164,  
 272, 273, 376, 377  
 Braestrup, C. B., 29  
 Bragance, B. de M., 247  
 Brahinsky, R. A., 253  
 Brahms, S., 363  
 Brambell, F. W. R., 544  
 Brand, E., 73  
 Brandenberger, E., 104  
 Brandama, K., 313  
 Brandt, J. L., 386  
 Brannon, E. S., 277  
 Bransby, E. R., 313  
 Brard, R., 103  
 Brasseur, H., 104  
 Bratton, R. W., 538, 539  
 Bratzler, J. W., 295  
 Braun, K., 355, 359, 360  
 Braun-Menendez, E., 327,  
 333  
 Brawner, H. P., 33  
 Brazil, M. A. B., 432  
 Brecher, G., 33  
 Brecher, G. A., 192, 347  
 Brecht, K., 192, 317, 320  
 Breckenridge, C. G., 181,  
 457  
 Breed, E. F., 388  
 Breed, E. S., 164, 334, 350  
 Bremer, F., 408, 432, 475  
 Brendler, S. J., 428, 447,  
 449  
 Brenner, S., 19  
 Bresnick, E., 192  
 Brewer, E. D., 476  
 Bricka, M., 20  
 Brickson, W. L., 82  
 Bridges, W. C., 163  
 Brierley, J. B., 460  
 Briggs, A. P., 163, 379  
 Briller, S. A., 278  
 Brink, F., 279  
 Brinkhous, K. M., 238  
 Brinkley, E. L., 226  
 Briseno-Castrejon, B., 507  
 Britton, S. W., 317, 351  
 Brizze, K., 322, 460  
 Brobeck, J. R., 140, 298,  
 449  
 Brocklebank, J. A., 352  
 Brod, J., 381  
 Broda, E. E., 489  
 Brodal, A., 480  
 Brodie, B. B., 150, 356  
 Brodie, T. G., 379  
 Brodsky, W. A., 159  
 Brody, D. A., 223, 460  
 Brody, S., 289, 290, 292,  
 293, 297  
 Brogden, W. J., 470  
 Broh-Kahn, R. H., 214,  
 520, 521, 522, 523  
 Brolin, S. E., 504  
 Brookhart, J. M., 426, 436  
 Brooks, C. McC., 399,  
 406, 407, 414, 415, 416,  
 417, 437  
 Brooks, J. W., 189  
 Brooks, M. M., 188  
 Brooks, R. E., 31  
 Brooks, S. C., 11, 12, 13  
 Brophy, D., 527  
 Browder, J., 434, 436  
 Brown, C. R., 384  
 Brown, D. D., *see* Denny-  
 Brown, D.  
 Brown, D. M., 86, 508  
 Brown, E. B., 185, 186  
 Brown, F., 184, 348  
 Brown, G. B., 90  
 Brown, H. R., 318  
 Brown, H. S., 224, 453  
 Brown, J. R., 191  
 Brown, M., 451  
 Brown, W. E., 542  
 Brown, W. M. C., 38  
 Browne, J. S. L., 157  
 Brubach, H. F., 193  
 Bruce, M. D., 385  
 Brücke, H., 460  
 Brues, A. M., 38, 85  
 Brühl, W., 378  
 Brumberg, E. M., 7  
 Brun, G. C., 238  
 Bruner, H. D., 193  
 Brush, F. H., 380  
 Brust, Z. Z., 388  
 Bryan, A. H., 192  
 Bryan, F. A., 29  
 Bryant, J. M., 361  
 Bryson, M. J., 380  
 Bubb, W., 277  
 Bubl, E. C., 82  
 Buchanan, A. R., 134,  
 449, 519  
 Bucher, G. R., 214, 227  
 Bucher, V., 435  
 Bucy, P. C., 424  
 Budy, A. M., 547  
 Bülbring, E., 332, 360,  
 384  
 Bull, G. M., 323, 391  
 Bull, H., 207  
 Bullock, F., 334  
 Bullock, T. H., 399, 452  
 Burch, B. H., 190  
 Burch, G., 161  
 Burch, G. E., 139, 324  
 Burchell, H. B., 192, 277,  
 279, 348, 359  
 Burchenal, J. H., 268  
 Buford, T. H., 352  
 Burger, J. W., 540  
 Burk, D., 18, 19, 302  
 Burkhardt, W. L., 191,  
 192, 277  
 Burks, A. L., 271  
 Burn, G. P., 12  
 Burn, J. H., 221, 332, 360,  
 384  
 Burnet, F. M., 47  
 Burnett, C. H., 157, 166,  
 352  
 Burnett, W. E., 334  
 Burns, C. M., 109  
 Burns, T. W., 157  
 Burnstein, M., 184, 455,  
 458  
 Burris, R. H., 301  
 Burrows, B. A., 154, 157,  
 166  
 Burstein, M., 248, 250,  
 252, 315, 316, 329, 332  
 Burton, A. C., 135, 311,  
 312  
 Burwell, C. S., 267, 277  
 Bush, F., 29  
 Busscher, G. de, *see* de-  
 Busscher, G.  
 Butcher, E. O., 104  
 Butcher, H. R., 193  
 Butler, C., 219  
 Butler, J. J., 246  
 Butt, H. R., 245  
 Büttner, K., 139  
 Butts, J. S., 82  
 Buy, H. du, *see* duBuy, H.  
 Byer, E., 361  
 Bylger, G. L., 123  
 Byrne, M., 255  
 Byrom, F. B., 390  
 Bywaters, E. G. L., 380

## C

- Caddell, H. M., 328  
 Calder, R. M., 188  
 Caldwell, A. B., 293  
 Caldwell, F. T., 192, 323  
 Calhoun, J. B., 541  
 Calkins, E., 307  
 Callan, H. G., 21  
 Callebaut, C., 360  
 Calvet, F., 20  
 Calvin, M., 77  
 Cameron, A., 222, 224  
 Cameron, A. T., 470

- Cameron, D. B., 193  
 Cameron, G. H., 29  
 Campbell, A. D., 506  
 Campbell, C. G., 333  
 Campbell, D. A., 215  
 Campbell, G. S., 184, 185, 186, 193, 456  
 Campbell, H. L., 550  
 Campbell, J. A., 108, 272, 277, 348  
 Canham, R. G., 334  
 Cannon, P. R., 71, 80, 295  
 Cantarow, A., 219, 505, 528, 547  
 Cappiello, M., 87, 509  
 Capo, L. R., 193, 331, 453  
 Cappellin, M., 103  
 Cargill, W. H., 109, 273, 375, 376, 379, 392, 529  
 Carlson, A. J., 228  
 Carr, C. J., 357  
 Carroll, R. T., 249  
 Carson, M. J., 352  
 Carter, J. R., 251  
 Cartier, P., 104, 105, 109  
 Cary, B. B., 189  
 Cary, M. K., 278, 317  
 Casady, R. B., 548  
 Casella, C., 280  
 Casida, L. E., 539, 541, 542  
 Casier, H., 452  
 Caspari, D., 47  
 Caspersson, T., 77  
 Cassels, D. E., 152, 269, 313, 355  
 Cassen, B., 29  
 Castle, W. B., 268  
 Castrejon, B. B., *see* Briseno-Castrejon, B.  
 Catchpole, H. R., 274  
 Cate, J. T., *see* Ten Cate, J.  
 Caveness, W., 450  
 Cayer, D., 38, 213  
 Celestino Dacosta, J., 101  
 Center, J. G. B., *see* Beebe-Center, J. G.  
 Cerceo, E., 547  
 Cerecedo, L. R., 550  
 Cerletti, A., 312, 459  
 Chadwick, L. E., 186, 188, 190, 274, 275, 276, 469  
 Chaikoff, I. L., 88, 385, 511, 525, 526, 528  
 Chalmers, A. K., 313  
 Chalmers, J. H., 456  
 Chamberlain, W. E., 28, 29  
 Chambers, E. L., 12, 13, 15  
 Chambers, F. W., 34  
 Chambers, J. W., 107  
 Chambers, R., 9, 10, 11, 14, 15, 17, 323  
 Chambers, W. H., 436  
 Chambers, W. W., 133  
 Chambon, Y., 547  
 Champeau, M. F., 107  
 Chance, M. R. A., 103  
 Chang, M. C., 122, 539, 540, 542, 545  
 Chang, H.-T., 409, 426, 432  
 Chang, P., 153  
 Chapanis, A., 485, 496, 497  
 Chapman, C. B., 322, 374  
 Chapman, D. W., 193  
 Chapman, E. M., 352, 453  
 Chapman, F. W., 279  
 Chapman, W. H., 34, 37  
 Chapman, W. P., 192, 314, 352, 429, 447, 453  
 Chardon, G., 316, 330, 379, 451  
 Chargaff, E., 249, 330, 455  
 Charipper, H. A., 511  
 Chase, H. B., 39  
 Chase, H. F., 191  
 Chasis, H., 370  
 Chassin, J. L., 391  
 Chatfield, P. O., 122, 182, 432, 457  
 Chatonnet, J., 314  
 Chattin, J. E., 541  
 Chauchard, P., 106, 192  
 Cheesman, D. F., 22  
 Chen, T. I., 237  
 Cheney, G., 245  
 Cheng, C.-P., 505  
 Cheng, P., 539, 541  
 Chenoweth, M. B., 225, 361  
 Chernoff, H. M., 129, 362  
 Chevallier, P., 250  
 Cheymol, J., 187, 270, 276  
 Chien, C. K., 424  
 Chilcott, M. E., 109  
 Child, G. P., 222, 223  
 Chimenes, A. M., 62  
 Chinard, F. P., 166  
 Chinn, H. I., 192  
 Chioldi, H., 180, 182, 192, 266  
 Chittum, J. R., 216, 223  
 Chor, H., 451  
 Chornyak, J., 192  
 Chow, B. F., 87, 509  
 Christensen, B. C., 272  
 Christensen, H. N., 78, 80, 82  
 Christensen, W. R., 131  
 Christiansen, E. G., 16  
 Christiansen, E. M., 266  
 Christy, H. W., 358  
 Churchill, E. D., 179  
 Churney, L., 361  
 Chusid, J. G., 424, 425  
 Ciaramelli, L. C., 157  
 Cisek, L. J., 159, 206, 381  
 Claesson, I. M., *see* Morning Claesson, I.  
 Claesson, L., 37, 508  
 Claff, C. L., 193  
 Clagett, O. T., 348  
 Clare, M. H., 434  
 Clark, G., 426, 541, 547  
 Clark, G. W., 426, 430  
 Clark, J. B., 61  
 Clark, J. K., 151, 163, 164, 183, 267, 273  
 Clark, J. W., 29  
 Clark, R. T., 192, 273  
 Clark, W. C., 222, 460  
 Clark, W. E. LeG., 428, 449, 475, 477, 479  
 Clark, W. G., 34  
 Clarke, B. G., 226  
 Clarke, R. W., 376  
 Claude, A., 19, 305  
 Clavert, J., 109, 110, 111  
 Cline, J. E., 328  
 Clouse, P. A., 325  
 Coblenz, B., 345  
 Code, C. F., 212, 213, 222, 223  
 Codie, J. F., 294  
 Coe, W. R., 545  
 Cohen, E. B., 251  
 Cohen, L., 29  
 Cohen, P. P., 77, 80  
 Cohen, S. M., 320, 350  
 Cohn, C., 322  
 Cohn, D. V., 529  
 Cohn, J. E., 327  
 Cohn, W. E., 72  
 Cole, H. H., 548  
 Cole, J., 426  
 Cole, J. W., 33, 249, 253  
 Cole, K. S., 400  
 Cole, W. H., 328  
 Coleman, D. H., 332, 384  
 Coleman, M. L., 384  
 Coles, M., 79  
 Colldahl, H., 186  
 Collet, A., 456, 459, 460  
 Collings, W. D., 334

- Collins, D. A., 101, 108,  
109, 225, 509, 528  
Collins, F. D., 478, 489  
Colowick, S. P., 86  
Colville, F., 154  
Comar, C. L., 105  
Combs, C. M., 432  
Comfort, J. E., 292  
Comfort, M. W., 221  
Commoner, B., 7  
Commons, R. R., 166  
Comroe, J. H., Jr., 192,  
267, 278  
Comstock, C. R., Jr., 192  
Conger, G. T., 456  
Conley, C. L., 238, 244,  
248, 252, 253  
Conn, J. W., 155, 164, 510,  
511, 520  
Conner, C. L., 385  
Connors, W. M., 11  
Conrat, J. F., *see* Fraenkel-  
Conrat, J.  
Consolazio, W. V., 129,  
266, 273, 275  
Constant, G., 352  
Conti, G., 454  
Conway, E. J., 147, 148,  
193, 207, 279  
Cook, H. A., 92  
Cooke, P. M., 436  
Cooke, R. E., 154  
Cooke, W. T., 373  
Cooper, K. E., 131, 319,  
322, 355  
Cooper, S. R., 453  
Cope, O., 152  
Copeland, D. E., 12  
Copley, A. L., 251, 255  
Copp, D. H., 105  
Coppedge, R. L., 304  
Corboz, J. R., 324  
Corcoran, A. C., 151, 329,  
334, 383, 388, 390  
Corday, E., 348  
Cordier, D., 182  
Cordier, G., 182  
Cordiez, E., 542  
Corey, E. L., 190  
Cori, C. F., 86, 521  
Cort, J. H., 383, 429, 433,  
448  
Co Tui, F. W., 153  
Cotzias, G. C., 166, 429,  
447  
Couillaud, 104  
Cournand, A., 183, 184,  
189, 191, 192, 265, 277,  
348, 350  
Coursand, A., 345  
Courtice, F. C., 274, 279,  
327  
Covian, M. R., 327, 333,  
519  
Cowan, R. L., 294  
Cowie, A. T., 511, 516,  
544  
Cowles, P. B., 17  
Cox, E. M., 192  
Cox, E. W., 127, 291  
Cox, W. C., 30  
Coy, F. E., Jr.  
Crabtree, W. V., 192  
Craddock, C. G., Jr., 35,  
248  
Craig, F., 272  
Craig, F. N., 123, 302, 377  
Craig, L. C., 72, 83  
Crampton, E. W., 107  
Crane, E. E., 208  
Cranston, R. W., 456  
Crass, G., 251  
Craver, B. N., 222, 224  
Crawford, M. P., 428  
Crescitelli, F., 399  
Cresson, S. L., 312  
Crew, F. A. E., 47  
Creysse, R., 270  
Crider, R. J., 211, 215  
Crismon, J. M., 122  
Croce, T. Lo M., *see* Lo  
Monaco-Croce, T.  
Croizat, P., 252  
Cronkite, E. P., 33, 34, 37  
Cronvich, J., 161  
Crosbie, J. M., 253  
Crosley, A. P., Jr., 163,  
164, 376  
Crosnier, R., 106  
Crowley, J. H., 193  
Cruck, S., 530  
Crumpton, C. W., 271,  
321, 459  
Crutchfield, A. J., 381  
Crutchfield, A. J., Jr., 158  
Cruz, W. O., 251, 266  
Caefko, I., 252  
Culbertson, J. T., 422  
Culbertson, J. W., 157,  
334, 352, 359, 453  
Cullen, S. C., 266  
Cullumbine, H., 327  
Culp, O. S., 540  
Cummine, H., 254  
Cupp, M. N., 34, 39  
Curry, J. J., 192  
Curtis, H. J., 311, 361, 400  
Curtis, L., 29  
Cushman, M., 160, 167  
Cutter, V. M., 49

## D

- Dacosta, J. C., *see* Celes-  
tino Dacosta, J.  
Dailey, M. E., 223  
Dale, W. M., 32  
Dallemagne, M. J., 101,  
102, 103, 104, 105, 110,  
111  
Dallenbach, K. M., 476  
Dalton, A. J., 19  
D'Alton, C. J., 154  
Daly, B. M., 255  
Daly, I. DeB., 184, 455,  
457  
Daly, M. M., 72  
Dam, H., 245, 247  
D'Amato, F., 48  
D'Amour, F. E., 189, 191,  
276  
Dan, K., 9  
D'Angelo, S. A., 275, 506  
Daniel, P. M., 373, 374,  
378, 379, 382, 384  
Danielli, J. F., 8, 103  
Danielson, W. H., 226  
Danowski, T. S., 148, 151,  
154, 166, 169, 170, 171  
Darling, R. C., 154, 192,  
269  
Darlington, C. D., 48  
Darmady, E. M., 391  
Darmon, S. E., 73  
Darrow, C. W., 431  
Darrow, D. C., 148, 154,  
167, 170  
Dartnall, H. J. A., 487,  
488, 489  
da Silva, E. M., 251  
Daubney, C. G., 313  
Dautrebande, L., 192  
Davenport, H. E., 270  
Davenport, H. W., 157,  
208  
David, M., 430, 432  
Davids, A. M., 545  
Davidson, J. N., 19  
Davidson, W. M., 190  
Davies, C. W., 246  
Davies, P. W., 279  
Davies, R. E., 207, 208  
Davis, B. D., 49  
Davis, C. N., 192  
Davis, C. T., 548  
Davis, G. D., 428, 447  
Davis, G. T., 539

- Davis, H. P., 539  
 Davis, J. H., 193  
 Davis, J. O., 161  
 Davis, J. R., 253  
 Davis, M. E., 547  
 Davis, R. E., 227  
 Davis, W. D., 333  
 Davison, R. A., 37  
 Daviss, H., 455  
 Davson, H., 485  
 Davy, L. S., 448  
 Dawes, G. S., 353  
 Dawson, I. M., 105, 107  
 Day, R., 121, 128  
 deAjuriag-Uerra, J., 432  
 Dean, R. B., 147  
 Deane, H. W., 506, 509  
     510  
 Deating, W. H., 222  
 Deasy, C. L., 72, 75, 77  
 DeBeer, E. J., 253  
 De Bruyn, P. P. H., 35  
 deBusscher, G., 192  
 de Elfo, F. J., 384  
 Deering, R., 139  
 Deese, J., 436  
 DeFriez, A. I. C., 449  
 De Gowin, E. L., 327  
 deGutierrez-Mahoney,  
     C. G., 425  
 Deitrick, J. E., 317  
 DeJongh, S. E., 506, 521  
 DeKoning, J., 548  
 de la Barreda, P., 333  
 De Lalla, V., 318  
 Delarue, R., 192  
 Delaunoy, A. L., 193  
 Delbrück, M., 62  
 Delgado, J. M. R., 134,  
     428, 429, 447  
 Dell, P., 449, 451  
 Della Santa, R., 107  
 DeLoach, A. W., 217  
 Delorme, E., 391  
 Delluva, A. N., 106  
 Delson, B., 543  
 De Maria, W. J. A., 109,  
     529  
 De Meio, R. H., 547  
 Demerec, M., 47, 48  
 de Molina, A. F., 333  
 Dempsey, E. W., 103, 510,  
     528  
 de Muylder, C., 382  
 de Nicola, P., 246  
 Denny-Brown, D., 425  
 Dent, C. E., 73  
 Derivaux, J., 109  
 Dermer, O.C., 470  
 De Robertis, E., 437, 528  
 DeSalva, S. J., 424  
 Dessauer, G., 30  
 De Takáts, G., 388, 389  
 Dethier, V. G., 469  
 Deuel, H. J., Jr., 122, 294,  
     295  
 Devi, P., 61  
 de Vries, A., 241, 243, 244,  
     250  
 de Vries, H., 489, 497  
 DeVries, K. J., 279  
 Dewey, V. C., 79, 92  
 Dexter, H., 346, 348  
 Dexter, L., 184, 267, 272,  
     277, 323, 362  
 Deyrup, I. J., 315, 353  
 Dhuner, K. G., 357  
 Diaz, C. J., *see* Jimenez  
     Diaz, C.,  
 Dicker, S. E., 154, 166,  
     168, 372  
 Dickman, S., 30, 31  
 Diczfalusy, E., 508  
 Didon, P., 378  
 Dikshit, P. K., 107  
 Dill, D. B., 186, 275  
 Dillon, W. G., 347  
 Dillon, W. H., 347, 349  
 Dipalma, J. R., 347  
 Dippell, R. V., 64  
 Dirken, M. N. J., 179, 184,  
     193, 265  
 Dishoeck, H. A. E. van,  
     *see* van Dishoeck,  
     H. A. E.  
 Dixon, F. J., 32, 36, 39  
 Dixon, K. C., 148  
 Dobbs, R. H., 391  
 Dobeln, M. V., 276  
 Dobriner, K., 546  
 Dobritz, O., 390  
 Dobson, R. L., 192, 278  
 Dobyns, B. M., 30  
 Dock, W., 379  
 Dodds, D. C., 223  
 Dodson, L. F., 390  
 Doesschate, J. ten, *see* ten  
     Doesschate, J.  
 Dole, V. P., 379, 380  
 Doles, H. M., 247  
 Dolgin, M., 361  
 Dominguez, R., 151  
 Donald, K. W., 190, 276  
 Donaldson, L. R., 32, 33  
 Dongen, K. van, *see* van  
     Dongen, K.  
 Donhoffer, S., 124  
 Donnelly, A. J., 36  
 Donner, K., 485, 488, 491,  
     492  
 Donnet, V., 323, 436, 458  
 Dooley, R., 33, 192  
 Doret, J. P., 460  
 Dorfman, A., 324  
 Dorfman, R. D., 546  
 Dornberger, G. R., 221  
 Dorrance, C., 192  
 Dorrance, G. M., 36  
 Dotter, C. T., 352  
 Dougherty, E. C., 105  
 Dougherty, I., 139  
 Douglas, C. G., 279  
 Douglas, D. M., 224  
 Douglas, J. C., 183, 192,  
     265, 267  
 Douglas, W. W., 314  
 Doupe, J., 313  
 Dow, J. W., 363  
 Dow P., 328, 352  
 Dow, R. S., 436  
 Dowdy, A. H., 28, 34  
 Dowling, C. V., 358, 458  
 Dowling, R., 190  
 Downey, H., 35  
 Downing, R., 192  
 Doxiadis, S. A., 152  
 Drabkin, D. L., 267, 515  
 Dragstedt, L. R., 209  
 Draper, W. B., 191, 192,  
     277  
 Dreiling, D. A., 221  
 Dresdale, D. T., 191  
 Dreyer, N. B., 215  
 Driggers, J. C., 105  
 Drill, V. A., 156  
 Drinker, C. K., 184, 193  
 Dripps, R. D., 311, 346  
 Droogleever, F. J., 431  
 Drury, D. R., 181  
 Dry, T. J., 192  
 Drye, J. C., 228  
 DuBois, E. F., 127, 291,  
     296, 297  
 duBuy, H., 19  
 Duckert, F., 220  
 Ducommun, P., 108  
 Dudley, R. A., 30  
 Duesberg, J. P., 255  
 Duff, I. F., 245  
 Duffner, G. J., 185  
 Dufrénoy, J., 17  
 Dufresne, O., 39  
 Dugal, L. P., 123, 186, 512  
 Duke, H., 184, 455, 457  
 Duke, H. N., 184  
 Duke, K. L., 541  
 Dulbecco, R., 62

Dumas, L. R., *see* Ribadeau-Dumas, L.,  
 Dumm, M. E., 513  
 Duncan, C. H., 456  
 Duncanson, D., 330, 352  
 Dunn, M. S., 73, 79, 80, 91  
 Dunn, R. W., 30, 105  
 Duntley, S. Q., 544  
 Duomarco, G., 347  
 Duomarco, J. L., 349  
 Durant, J., 252  
 Durant, T. M., 356  
 Dureuil, M., 519  
 Duryee, W. R., 10, 12  
 Dustin, E., 193  
 Dustin, P., Jr., 17  
 Dutt, R. H., 542  
 Dutta, N. C., 106  
 du Vigneaud, V., *see* Vigneaud, V. du  
 Dvoskin, S., 524  
 Dyniewicz, H. A., 226  
 Dziemian, A. J., 378  
 Dziewiatkowski, D., 227

## E

Eakin, R. E., 79  
 Eames, R. P., 29  
 Earl, A., 222  
 Earle, D. P., Jr., 151, 163  
 Earle, W. R., 85  
 Early, D. F., 431  
 East, J., 547  
 Eastman, H. D., 191  
 Eather, K. F., 311  
 Eaton, J. C., 359  
 Ebaugh, F. G., 132  
 Ebeling, J., 313, 317  
 Ebert, R. V., 184, 348  
 Eccles, J. C., 399, 406, 407, 414, 415, 416, 417, 437, 508  
 Eckel, R., 346, 358, 458  
 Eckenhoff, J. E., 188, 271, 272  
 Eckman, I., 275  
 Eckman, M., 275  
 Eckstein, R. W., 346, 358, 458  
 Ectors, L., 475  
 Edelman, I. S., 164  
 Edelmann, A., 37, 190, 507  
 Eder, H. A., 166, 268  
 Ederstrom, H. E., 326  
 Edholm, O. G., 192, 267, 320, 328, 330, 350, 352

Edmonds, D. G., 325  
 Edsall, J. T., 254  
 Edwards, C. T., 207  
 Edwards, E. A., 544  
 Edwards, L. E., 207  
 Effersoe, P., 386  
 Eggleston, L. V., 77, 79, 80, 148  
 Egner, W., 253  
 Ehrenhaft, J. L., 192, 279  
 Ehrensvar, G., 73  
 Ehrich, W. E., 253, 505  
 Eichelberger, L., 154, 171  
 Eichhorn, R. D., 191  
 Eichna, L. W., 128, 163  
 Eisenberg, L., 121, 128, 319  
 Eiseman, A. J., 152  
 Eisenmenger, W. J., 166  
 Elam, J. O., 191, 192, 278, 279  
 Elam, W. N., Jr., 192  
 Elbinger, R. L., 78, 80, 82  
 Eldred, E., 436  
 Elghammer, R. M., 253  
 Elfo, F. J. de, *see* de Elfo, F. J.  
 Elion, G. B., 82  
 Eliot, J. W., 124, 126, 157  
 Elkin, M., 229, 312  
 Elkinton, J. R., 148, 151, 152, 154, 157, 163, 164, 166, 168, 169, 170, 171  
 Ellinger, F., 37, 38, 505  
 Ellinger, G. F., 346  
 Elliott, H. W., 122  
 Elliott, K. A. C., 188, 299, 302, 431  
 Elliott, R., 471  
 Ellis, F. P., 190  
 Ellis, M. E., 157  
 Elman, R., 326  
 Elsberg, C. A., 476  
 Elsdon, S. R., 72  
 Elster, S. K., 324  
 Eltzholtz, D. C., 33, 34  
 Elvehjem, C. A., 81, 82  
 Elwell, L. H., 189  
 Ely, J. O., 7, 10, 38  
 Emerson, C. P., 325  
 Emerson, G., 550  
 Emerson, G. A., 225  
 Emerson, K., Jr., 157, 379, 380  
 Emerson, M. R., 49  
 Emerson, S., 56, 78  
 Emery, F. E., 111  
 Emmelin, N., 225, 353, 452

Emmens, C. W., 539  
 Emslie, A. R. G., 106, 107, 108  
 Endicott, K. M., 33  
 Engel, F. L., 513, 514, 515  
 Engel, G. L., 277  
 Engel, M. G., 513  
 Engle, E. T., 36, 545  
 Engström, A., 10, 11  
 Engstrom, W. W., 88  
 Enloe, C. F., 39  
 Enselme, J., 270  
 Entenman, C., 385  
 Ephrussi, B., 62  
 Eppinger, E. C., 277  
 Eppright, M., 550  
 Epstein, F. H., 331  
 Epstein, J. A., 181, 429, 430, 447, 456  
 Epstein, M. A., 266, 275  
 Eränkö, O., 315  
 Erickson, D. M., 188  
 Erickson, T. C., 475, 481  
 Ermala, P., 38  
 Ershoff, B. H., 122  
 Erspamer, V., 225  
 Eschenbrenner, A. B., 36  
 Escher, D. J. W., 164  
 Essenberg, J. M., 36  
 Essex, H. E., 347  
 Essig, C. F., 450  
 Estremera, H. R., 106  
 Etsten, B., 191  
 Euler, C. v., 458  
 Euler, U. S. v., 184, 210, 330, 455  
 Evans, A. M., 101  
 Evans, D. H. L., 459  
 Evans, G., 514  
 Evans, G. T., 138, 188, 189  
 Evans, H. J., 280  
 Evans, H. M., 86, 87, 92, 101, 107, 108, 109, 157, 508, 509, 515, 528, 549, 550  
 Evans, J. A., 334  
 Evans, J. D., 301, 302  
 Evans, J. M., 277  
 Evans, T. C., 29  
 Evelyn, K. A., 453  
 Everard, B. A., 241  
 Everett, J. W., 449, 504, 508, 513, 543  
 Eversole, S. L., 320  
 Eversole, W. J., 157  
 Ewing, P. L., 225  
 Eylenburg, E., 246

## F

- Faber, M., 330, 455  
 Fabre, J., 107  
 Fahey, J. L., 239, 241, 243, 245  
 Faik, S., 224  
 Failla, G., 28  
 Failley, R. B., 363  
 Fainer, D. C., 191  
 Fairfield, J., 122, 355  
 Fairley, J. L., 56  
 Fairman, D., 475  
 Falconer, D. S., 470  
 Falkenheim M., 105  
 Faltz, E. L., 272  
 Fankuchen, I., 106  
 Fantl, P., 241, 242, 246, 255  
 Farah, A., 163, 225  
 Farber, H. R., 193  
 Farber, S. J., 151, 163  
 Farber, V. B., 276  
 Farnsworth, E. B., 165, 166  
 Farrar, B., 513, 514  
 Farrar, C. H., 331  
 Farris, E. J., 37, 541  
 Fasciolo, J. C., 182, 192, 266  
 Fastier, F. N., 357  
 Faulconer, A., Jr., 193  
 Favre-Gilly, J., 239, 242, 250, 252, 256, 270  
 Fawcett, D. W., 522  
 Feaver, E. R., 73, 91  
 Fegler, J., 270  
 Feigelman, H., 77  
 Feigen, G. A., 312  
 Feil, H., 363  
 Feindel, W. H., 424, 437  
 Feld, A. E., 12  
 Feld, E. A., 399  
 Feld, M., 428  
 Feldberg, W., 223, 225, 353  
 Felder, D. A., 389  
 Feldman, M., 329, 351, 360  
 Feldman, M., Jr., 189, 192  
 Fellers, F. X., 151, 152  
 Fenn, W. O., 180, 185, 186, 190, 192, 266, 273, 275, 276, 277  
 Fenner, F., 47  
 Ferayorni, R. R., 212  
 Feremutsch, K., 433  
 Ferger, M. F., 83  
 Ferguson, D., 130  
 Ferguson, J. H., 242, 249  
 Ferguson, J. K. V., 279  
 Ferguson, J. K. W., 192, 278  
 Ferkel, R. L., 38  
 Fernández, D., 456  
 Ferraro, L. R., 152  
 Ferrer, J. M., 213  
 Ferrer, M. I., 157, 345  
 Ferris, B. G., Jr., 131  
 Ferris, D. O., 391  
 Ferris, E. B., 277, 278, 334, 388  
 Ferris, E. B., Jr., 388  
 Ferry, J. D., 21  
 Fetcher, E. S., 125, 130  
 Feuer, I., 192  
 Feyrer, E., 192  
 Fiala, S., 18  
 Fidler, E., 251  
 Fiehrer, A., 250, 254  
 Field, E. J., 460  
 Field, J., 134  
 Field, J. B., 34, 247  
 Fields, M., 294  
 Fields, W. S., 433  
 Fieser, L. F., 546  
 Fieser, M., 546  
 Finas, C., 456  
 Finch, C., 268  
 Finerty, J. C., 507  
 Fink, A., 128  
 Fink, K., 525  
 Fink, R. M., 525  
 Finkelman, I., 451  
 Finkelstein, M., 546  
 Finlayson, D. M., 192, 278  
 Fisch, S., 253  
 Fischer, A., 84  
 Fischer, C. J., 103  
 Fischer, E. H., 220  
 Fischer, F., 277  
 Fischer, K. H., 449  
 Fischer, P. F., 384  
 Fiset, P. E., 186  
 Fish, H. S., 471  
 Fisher, B., 244  
 Fisher, J. A., 387  
 Fisher, M. B., 266  
 Fisher, R. R., 424  
 Fishler, M. C., 40  
 Fishman, J. B., 86, 508  
 Fishman, W. H., 153  
 Fitcher, P. H., 333  
 Fitzgerald, O., 207, 214  
 Fitzgerald, P. J., 251  
 Fitzpatrick, H., 314, 350  
 Fitzpatrick, T., 307  
 Flamant, F., 498  
 Flasher, J., 334  
 Fleck, L., 251  
 Fleisch, A., 312  
 Fleischmann, W., 123  
 Fleisher, J. H., 226  
 Flemister, S. C., 279  
 Flett, J., Jr., 154, 170  
 Flickinger, D., 192  
 Flieg, W., 348  
 Fling, M., 54, 82  
 Flink, E., 157  
 Flock, E. V., 528  
 Flynn, J. E., 256  
 Fogelman, M. J., 217  
 Foldes, E., 386  
 Foley, J. M., 278  
 Foley, J. O., 471  
 Folger, H. T., 8  
 Folk, B. P., 193  
 Folk, G. E., 123  
 Folkow, B., 315, 330, 352, 358, 449, 455  
 Folley, S. J., 516  
 Foltz, E. L., 128, 358  
 Fonio, A., 250  
 Fönss-Bech, P., 108  
 Foote, R. H., 538  
 Forbes, A., 432  
 Forbes, T. R., 546, 547  
 Ford, C. E., 48  
 Forro, F., Jr., 31  
 Forsander, C. A., 277  
 Forsgren, A., 322, 374  
 Forsham, P. H., 157, 510  
 Forster, R., 2nd, 121, 128, 319  
 Forster, R. E., 2nd, 131  
 Forti, L., 181  
 Fortier, C., 186  
 Foster, D., 476  
 Foster, R. F., 32, 33  
 Foster, J. F., 254  
 Foster, R. H. K., 253  
 Foulks, J., 371  
 Fowell, D. M., 163, 277, 379  
 Fowler, E. F., 388, 389  
 Fowler, R. C., 192  
 Fowler, W. S., 183, 192, 267  
 Fox, C., 275  
 Fox, C. A., 424, 429, 480  
 Fox, C. L., Jr., 165, 166, 171, 385  
 Fox, H. M., 274  
 Fox, S. W., 82  
 Fraenkel, G., 79  
 Fraenkel-Conrat, J., 528

- Frame, B., 156  
 Frame, E., 251  
 France, O., 37  
 Franck, C., 182, 193, 322,  
 329, 378, 458  
 Franck, J., 146  
 Frank, E., 189, 330  
 Frank, L. K., 422  
 Franke, F. E., 139  
 Franke, R. E., 265, 267  
 Franklin, A. L., 79, 526  
 Franklin, K. J., 373, 374,  
 378, 379, 382, 384  
 Frantz, I. D., Jr., 72, 73,  
 75, 77, 85, 90, 91  
 Frantz, J. A., 124  
 Frantz, M., 17  
 Frantz, M. J., 511  
 Fraps, R. M., 542, 546  
 Frazer, J. F. D., 87  
 Frazier, L. E., 295  
 Fredericq, P., 256  
 Freed, H., 432  
 Freed, J. H., 37  
 Freed, S. C., 311  
 Freedman, A. M., 453  
 Freeman, M. E., 324  
 Freeman, S., 220  
 Freeman, W., 428, 449  
 Freis, E. D., 153, 325, 352  
 French, C. E., 294  
 French, C. R., 317  
 French, D. M., 192, 376  
 French, J. D., 424  
 French, T. H., 516  
 Frey, E., 435  
 Frey, K., 379  
 Freyburger, S. W., 495  
 Freyburger, W. A., 356  
 Freyhan, F. A., 429, 459  
 Freytag, R. M., 108  
 Frey-Wyssling, A., 21  
 Freud, J., 36  
 Frew, J. L., 335  
 Frick, P., 243  
 Friedell, H. L., 326  
 Frieden, E., 83  
 Friedberg, F., 73, 74, 75,  
 79, 86, 90  
 Friedburg, C. K., 165  
 Friedeman, T. E., 276  
 Friedgood, H. B., 546  
 Friedkin, M., 306  
 Friedlander, R. D., 247  
 Friedman, A., 124, 523  
 Friedman, C. L., 384, 388  
 Friedman, H., 191, 192,  
 274  
 Friedman, M., 311  
 Friedman, M. H. F., 221,  
 229  
 Friedman, M. M., 152  
 Friedman, S. M., 333, 384,  
 388  
 Friend, F., 219  
 Fries, N., 48, 49, 56  
 Friesen, S. R., 216  
 Friis, N. P., 392  
 Frings, H., 472  
 Fritschy, W., 252  
 Fronius, E. K., *see* Kerpel-  
 Fronius, E.  
 Frost, J., 315, 330, 352,  
 358, 455  
 Frost, J. W., 108  
 Fruton, J. S., 75, 81  
 Fuchs, F., 373  
 Fuchs, J. E., 192  
 Fugo, N. W., 547  
 Fuhrmann, G., 370  
 Fujita, M., 399  
 Fuller, F. D., 128  
 Fulton, J. F., 428, 432,  
 447, 448, 449, 462, 474  
 Funkenstein, D. H., 450  
 Fuoss, R. M., 399  
 Furchgott, R. F., 299, 387  
 Furlow, L. T., 449  
 Furth, J., 26  
 Fuster, B., 430  
 Futch, E. D., 350  
 Futch, P. H., 384  
  
**G**  
 Gaarenstroom, J. H., 506,  
 521  
 Gabrilove, J. L., 505  
 Gabrio, B. W., 110  
 Gaebler, O. H., 509  
 Gagge, A. P., 139  
 Gaillard, P. J., 85  
 Gairdner, D., 152, 256  
 Gál, I., 191  
 Galambos, R., 192  
 Galdman, D. E., 273, 274  
 Galdson, M., 265  
 Galdston, C. G., 266  
 Galdston, M., 163, 184,  
 193  
 Gale, E. F., 71, 78, 80  
 Galeone, A., 246  
 Gallagher, J. P., 436  
 Gallego, A., 399  
 Galvão, P. E., 127, 290,  
 291  
 Gamble, A. H., 154, 170  
 Gamble, J. L., 317, 351  
 Gantt, W. H., 192  
 Garb, S., 361  
 Garces, B. C., 249  
 Garces, S. M., 249  
 Garcia, J. F., 509, 516  
 Garcia, J. P., 122, 432  
 García Ramos, J., 400,  
 404, 406, 423  
 Gardell, S., 252  
 Gardner, E., 182  
 Gardner, W. D., 429  
 Gardner, W. U., 110, 507  
 Garrett, F. D., 437  
 Garrett, S. S., 544  
 Garst, J. B., 546  
 Garvin, J. S., 432  
 Gasser, H. S., 401, 414  
 Gastaut, H., 432  
 Gaston, W., 33, 253  
 Gaston, E. A., 225  
 Gauben, W. G., 511  
 Gaudino, M., 151  
 Gauer, O., 271, 279, 317,  
 351  
 Gaunt, R., 158  
 Gay, D. M., 37  
 Gay, N., 48  
 Gay, J. R., 424  
 Geberg, A., 383  
 Gelfan, S., 190, 328  
 Gellhorn, E., 192, 424,  
 426, 430, 431, 432, 433  
 Gemmill, C. L., 276  
 Gemzell, C. A., 508, 512  
 Genecin, A., 163, 164  
 Georg, J., 182, 385  
 George, C., 255  
 Geraci, J. E., 192, 278,  
 279  
 Gerbi, C., 382  
 Gerebtzoff, M. A., 435,  
 473, 474, 475  
 Gerendas, M., 248, 252  
 Gergely, J., 526  
 Gerhardt, E., 474  
 Gerheim, E. B., 249  
 German, L. L., 29  
 Gernandt, B., 417, 451,  
 490, 491, 492, 493  
 Gershbein, L. L., 212, 221  
 Gesell, R., 417, 437  
 Geschwind, I., 86, 87, 509  
 Getz, B., 435, 451  
 Gey, G. O., 19, 20, 85  
 Ghosh, D., 539  
 Giacomino, N. J., 109  
 Gibbon, M. H., 193  
 Gibbs, E. L., 271, 430

- Gibbs, F. A., 192, 271, 430, 432  
 Gibson, J. G., 269  
 Gibson, Q. H., 268, 269  
 Giese, A. C., 126  
 Gilbert, C., 547, 551  
 Gilbreath, J. C., 539  
 Gilchrist, M., 267, 268  
 Gilder, H., 302  
 Giles, N. H., 53  
 Gilg, E., 214  
 Gillespie, E. C., 325, 543  
 Gillman, J., 547, 551  
 Gillman, T., 551  
 Gillman, Y., 385  
 Gilly, J. F., *see* Favre-Gilly, J.  
 Gilman, A., 171, 357, 371  
 Gilmore, L. O., 541  
 Gilmire, R. C., 294  
 Gilmour, J. R., 109  
 Gilson, J. C., 180  
 Ginsburg, E., 275  
 Ginther, G. B., 513  
 Girard, P., 106  
 Giroud, A., 107, 507  
 Gittleman, I. F., 107  
 Glantz, P. F., 538  
 Glanzmann, E., 108  
 Glarborg, E., 121  
 Glass, G. B. J., 214  
 Glass, S. J., 548  
 Glasser, O., 328, 329  
 Glasser, S. M., 38  
 Glavind, J., 247, 256  
 Glees, P., 426, 432  
 Glenn, W. W. L., 312  
 Glickman, N., 140, 294, 298  
 Glock, G. E., 102  
 Glover, J., 486  
 Glover, R. M., 189, 276  
 Glueck, H. I., 255  
 Glynn, L. E., 103  
 Godfrey, L., 157, 192  
 Godina, G., 101  
 Goettsch, M., 550  
 Goetz, R. H., 331, 389  
 Goetzl, F. R., 206, 476  
 Gold, T., 423  
 Goldberg, H., 378  
 Goldberg, L., 192  
 Goldberg, S. L., 228  
 Goldblatt, H., 333, 386, 387, 390  
 Goldblith, S. A., 31  
 Golden, A., 376  
 Golden, H., 124  
 Goldenberg, M., 330, 352, 455  
 Goldensohn, E. S., 192  
 Golding, J. S. R., 104  
 Goldman, D. E., 400  
 Goldman, M. L., 333  
 Goldman, S., 424  
 Goldschmidt, M., 206, 476  
 Goldsmith, E. D., 528  
 Goldsmith, H. H., 28  
 Goldscheider, G., 36  
 Goldstein, M., 522  
 Goldstein, R., 243, 244, 250  
 Goldthwait, D. A., 125  
 Gollan, F., 153, 186, 333, 386, 387  
 Gollwitzer-Meier, K., 332  
 Goltra, E. R., 191  
 Golubew, W. Z., 383  
 Gonzalez, T. A., 40  
 Goodale, W. T., 272, 359, 360  
 Goodell, H., 138  
 Goodeve, C. F., 489  
 Goodfriend, J., 352  
 Goodgal, S. H., 48  
 Goodman, B., 251  
 Goodman, D., 226  
 Goodman, J., 189  
 Goodman, M. J., 357  
 Goodman, L. S., 453  
 Goodrich, B. E., 192  
 Goodwin, C. W., 424  
 Goodwin, T. W., 486  
 Goodwin, J. F., 353  
 Goodwin, W. E., 384  
 Goodyer, A. V. N., 159, 311  
 Goormaghtigh, N., 390  
 Gopalkrishna, A., 541  
 Göpfert, H., 329  
 Gorbatone, O., 274  
 Gorbatow, O., 192  
 Gordman, A., 37  
 Gordan, G. S., 271  
 Gordon, A. H., 72  
 Gordon A. S., 511  
 Gordon, B., 180, 189  
 Gordon, E. E., 192, 269  
 Gordon, E. S., 79  
 Gordon, G. S., 86  
 Gordon, H. H., 171  
 Gorham, L. W., 161  
 Gorman, A. E., 28  
 Gosselin, R. E., 123, 458  
 Göthlin, G., 489  
 Gould, J., 357  
 Govaerts, J., 110, 111  
 Gover, M., 313  
 Gow, R., 171  
 Gowdey, J. F., 363  
 Grabar, P., 18  
 Grace, W. J., 229  
 Graff, S., 255  
 Graham, C. H., 499  
 Graham, H. T., 399  
 Graham, J. D. F., 331  
 Graham, S. E., 433  
 Granados, H., 247  
 Grand, C. G., 10  
 Grandjean, E., 179, 330  
 Grandpierre, R., 182, 183, 193, 322, 329, 378, 458  
 Granick, S., 267  
 Granit, R., 417, 485, 486, 488, 489, 490, 491, 492, 493, 498  
 Grant, F. C., 271  
 Grant, H. E., 352  
 Grant, R., 134, 219, 227  
 Grant, W. C., 268, 279  
 Grau, S., 361  
 Gray, E. H., 314, 448  
 Gray, F. D., 277  
 Gray, J. S., 207  
 Gray, J. A. B., 455  
 Gray, L. H., 32  
 Graybiel, A., 190  
 Greco, G., 278  
 Green, A. A., 238  
 Green, C., 249  
 Green, D. M., 158, 163, 332, 333, 384  
 Green, H. D., 331  
 Green, J. R., 428, 449  
 Green, N. D., 390  
 Green, R. S., 316, 355  
 Greenbaum, A. L., 516  
 Greenberg, A., 156  
 Greenberg, D. M., 73, 74, 75, 77, 79, 86, 90  
 Greenberg, L. A., 193  
 Greenblatt, M., 450  
 Greenblatt, R. B., 544  
 Greene, D. G., 185, 330, 352  
 Greenfield, A. D. M., 312, 322  
 Greenfield, M. M., 39  
 Gregoire, F., 272  
 Gregory, J. D., 72, 83  
 Gregory, R., 350, 390  
 Gregersen, M. I., 154, 168, 206, 273, 274, 328  
 Greif, R. L., 166  
 Greig, M. A., 299

Greenman, L., 148, 151, 171  
 Greenstein, J. P., 31, 90, 91  
 Greenwald, I., 103  
 Greep, R. O., 87, 103, 506, 509, 510, 521  
 Griesbach, W. E., 529  
 Griffin, A. C., 92  
 Griffith, F. R., Jr., 296  
 Griffith, R. S., 124  
 Grimson, K. S., 216, 223, 334, 453  
 Grindlay, J. H., 221, 224, 228, 324  
 Grinstein, M., 76  
 Grisolia, S., 77, 80  
 Griswold, H. E., 272, 277, 348  
 Grob, D., 253, 453  
 Grodins, F. S., 182, 276, 277  
 Groedel, F. M., 362  
 Groff, A. E., 272  
 Groff, R. A., 320, 321, 459  
 Grollman, A., 157, 333  
 Groody, M., 108  
 Groom, D. L., 279  
 Grosch, D. S., 541  
 Gross, A., 330, 379, 451  
 Gross, E. G., 246  
 Gross, J., 526, 527  
 Grossault, S., 106  
 Grossberg, A., 215  
 Grossman, B. J., 253  
 Grossman, J., 164  
 Grossman, M., 325  
 Grossman M. I., 205, 206, 209, 211, 212, 213, 214, 216, 217, 218, 220, 222, 223, 227, 228, 449, 460, 477  
 Grossman, M. S., 190, 276  
 Grover, R. F., 192, 348  
 Gruber, C. M., 223  
 Gruber, C. M., Jr., 223  
 Gruenstein, M., 218  
 Gruhn, J. G., 386  
 Grüneberg, H., 47  
 Grundfest, H., 399, 406  
 Grunke, W., 252  
 Guba, F., 254  
 Gueguen, J., 246  
 Guest, M. M., 240, 254, 255  
 Guilhem, J., 183  
 Guirard, B. M., 50, 53  
 Gugle, L. J., 193

Gullickson, G., 191, 192, 278  
 Gullickson, G., Jr., 192  
 Gullickson, M. J., 215  
 Gump, H., 33  
 Gunton, R. W., 274, 327  
 Gurdjian, E. S., 192, 271  
 Gustafsson, A., 48  
 Gustafson, G. E., 380  
 Guthrie, T. C., 451  
 Gutman, A. B., 102  
 Gutman, E. B., 102  
 Gutmann, H., 269  
 Guttman, W., 250  
 Guyton, A. C., 318, 321  
 Gyarlaf, K., 192, 431  
 Gyorgy, P., 222  
 Györgyi, A. S., *see* Szent-Györgyi, A.

## H

Haagen-Smit, A. J., 72, 74, 75, 77, 546  
 Haas, F. O., 58, 60, 61  
 Hackel, D. B., 123, 272, 359, 360  
 Haddy, F. J., 184  
 Haeger, K., 315, 352, 455  
 Hafkenschiel, J. H., 188, 271, 272, 320, 321, 459  
 Hagedorn, A. B., 253  
 Hagen, P. S., 247  
 Haig, C., 497, 499  
 Haimovici, H., 389  
 Haist, R. E., 322, 520  
 Hajdu, I., 192  
 Haladay, D. A., 453  
 Halbeisen, W. A., 223  
 Hald, P. M., 145  
 Hale, E. H., 217  
 Haley, T. J., 323  
 Halkerson, J. M., 522  
 Hall, A. D., 166  
 Hall, A. R., 470  
 Hall, C. A., 156  
 Hall, C. E., 254  
 Hall, F. G., 187  
 Hall, J. F., 125, 130  
 Hall, K., 548  
 Hall, L. E., 517  
 Hall, P. W., 164, 322  
 Hall, V. E., 134, 451  
 Hall, W. E., 529  
 Halperin, M. H., 273, 334, 359, 377, 453  
 Halpern, L., 436  
 Halse, T., 255  
 Halstead, W., 428  
 Hamann, A., 219  
 Hamburger, F. A., 485  
 Hamet, R., 453  
 Hamilton, G. T. C., 316, 453  
 Hamilton, H. E., 327  
 Hamilton, J. F., 349  
 Hamilton, J. G., 27, 105  
 Hamilton, P. B., 379, 381  
 Hamilton, W. F., 163, 277, 345, 352, 379  
 Hamilton, W. F., Jr., 277  
 Hammer, E. R., 499  
 Hammer, J., 216  
 Hammill, J. F., 313  
 Hammond, H., 278  
 Hammond, M., 359  
 Hammond, M. R., 14  
 Hampson, J. L., 436, 450  
 Hancox, N. M., 102  
 Handelsman, J. C., 272, 277, 348, 359  
 Handler, P., 109, 529  
 Handley, C. A., 357  
 Hanks, J. H., 85  
 Hansen, E. T., 417  
 Hansen, L. A., 247  
 Hanser, P. J., 380  
 Hanson, M. E., 206, 210, 217, 449, 477  
 Happ, W. P., 124  
 Hardenbergh, E., 191, 193, 277, 315, 346, 455, 458  
 Hardgrove, M., 334  
 Harding, D., 8  
 Harding, W. M., 79, 82  
 Hardt, L. L., 211  
 Hardy, J. D., 120, 121, 127, 130, 138, 289, 291, 296, 297  
 Hare, K., 151, 152, 369, 370  
 Hare, R., 369  
 Hare, W., 227, 369  
 Harger, R. N., 193  
 Hargreaves, B., 248  
 Harlow, H. F., 428  
 Harman, P. J., 455  
 Harmel, M. H., 271, 272, 321, 459  
 Harpuder, K., 505  
 Harreveld, A. van, *see* van Harreveld, A.  
 Harrington, D. O., 457  
 Harris, D. H., 323  
 Harris, E. J., 12  
 Harris, G. W., 381, 382, 433, 449, 504

- Harris, R., 355  
 Harris, S. C., 276  
 Harrison, D. C., 268, 269  
 Harrison, H. C., 105  
 Harrison, H. E., 105  
 Harrison, R. J., 547  
 Hart, D., 546  
 Hart, G. H., 548  
 Hartert, H., 255  
 Hartiala, K., 218  
 Hartline, H. K., 490, 491  
 Hartman, F. W., 192, 278, 279  
 Hartmann, J. F., 227  
 Hartmann, R. C., 238, 252, 253  
 Hartridge, H., 471, 492, 496  
 Harvey, A. M., 399, 453  
 Harvey, R. M., 345  
 Hasama, B., 481  
 Hassler, R., 428  
 Hastings, A. B., 73, 80  
 Hastings, N., 314, 448  
 Hatch, T., 192  
 Hatch, T. F., 296, 297  
 Haterius, H. O., 123, 458  
 Haugaard, G., 73  
 Haugaard, N., 521  
 Hawirko, R., 59, 60  
 Hawkinson, V., 76  
 Hawley, E. E., 295  
 Hawley, J. G., 347  
 Hawn, C. van Z., 21, 254  
 Hawthorne, H. R., 228  
 Hayashi, T., 21  
 Hayes, D. W., 331  
 Haymaker, W., 192, 503  
 Hayne, R., 434, 448  
 Haynes, F. W., 184, 267, 277, 323, 346, 348  
 Hayter, R., 185  
 Heagan, B. S., 274  
 Heagy, F. C., 135  
 Heath, C. W., 268  
 Heath, H. D., 128  
 Heath, R. G., 428  
 Hebb, C. O., 184, 192, 455, 457  
 Hécaen, H., 430, 432, 461  
 Hecht, L., 147  
 Hecht, M., 499  
 Hecht, S., 497, 498  
 Hechter, O., 512  
 Hedlund, D. S., 327  
 Heemstra, A. H., 265  
 Heemstra, H., 184, 193  
 Heerhaber, I., 183  
 Heersma, J. R., 226  
 Hege, J. R., 390  
 Hegnauer, A. H., 123, 278, 458  
 Hegsted, D. M., 153, 327  
 Heilbrunn, L. V., 8, 15  
 Heilesen, B., 293  
 Heinbecker, P., 295, 509  
 Heindl, I. A., 247  
 Heitman, H., Jr., 297  
 Hellems, H. K., 184, 323, 346, 348, 362, 363  
 Heller, H., 160, 167  
 Heller, J. H., 386  
 Hellerstein, H. K., 361  
 Hellman, L., 518  
 Helmer, O. M., 387  
 Helmholtz, H. F., 183  
 Helmholtz, H. F., Jr., 192  
 Hemeon, W. C. L., 192  
 Hemingway, A., 138, 185, 192, 193  
 Hempelmann, L. H., 37, 39  
 Hems, R., 77, 80  
 Hench, P. S., 516, 517  
 Henderson, J. B., 189, 276  
 Henderson, L. M., 82  
 Henderson, N., 109  
 Hendley, C. D., 269  
 Hendrick, C., 294  
 Hendricks, J. B., 108  
 Hendrickson, I., 189, 328  
 Hendricky, J., 311  
 Hendrix, J. P., 453  
 Henneman, E., 433, 436, 450, 474  
 Henny, G. C., 105  
 Henriques, F. C., 121  
 Henriquez, O. B., 548  
 Henriquez, S. B., 548  
 Henry, J. P., 189, 271, 279, 317, 328, 351  
 Henry, R., 270  
 Henschel, A., 153, 322, 374, 456  
 Henson, M., 274  
 Heraux, 192  
 Herber, F. J., 276  
 Herbert, P. A., 379  
 Herbert, P. H., 294  
 Hermann, R. G., 192  
 Hermans, J. J., 23  
 Herrick, J. F., 121, 228  
 Hershey, A. D., 61  
 Hertz, H., 401  
 Hertzman, A. B., 130, 139, 297, 317  
 Hervé, A., 34  
 Herxheimer, H., 193, 314, 355  
 Hess, M., 219  
 Hess, W. R., 435, 448, 450, 461  
 Hesselbach, M. L., 18  
 Hesser, C. M., 182, 193  
 Heston, W., 47  
 Hetényi, G., Jr., 192, 526  
 Hevesy, G., 38, 105  
 Hewer, T. F., 387  
 Heymans, C., 193, 314, 452, 458  
 Hiatt, E. P., 377  
 Hickam, J. B., 272, 273, 322, 324, 376, 379  
 Hicks, J. H., 391  
 Hiestand, W., 123, 128  
 Higginbottom, C., 61  
 Higgins, J. R., 223  
 Highman, B., 192  
 Hightower, N. C., 223  
 Hill, A. V., 318, 404  
 Hill, H. V., Jr., 216  
 Hill, B. R., 546  
 Hill, D. K., 399  
 Hill, E. J., 216  
 Hill, J. M., 251  
 Hill, R. M., 134, 449, 519  
 Hill, T. S., 153  
 Hillarp, N., 9, 449, 454, 504, 508  
 Hiller, A., 166, 266, 380  
 Hilliard, I. M., 192, 278  
 Hillier, J., 20  
 Hills, A. G., 157  
 Hiltén, J. G., 371  
 Himmelstein, A., 184, 185, 191, 265, 277, 348, 350  
 Himsworth, J., 522  
 Himwich, H. E., 271, 450, 453  
 Hines, H. M., 29, 131, 540  
 Hingerty, D., 147, 148  
 Hinkle, L. E., Jr., 225, 456  
 Hinshaw, J. R., 454  
 Hin Tjio, J., 48  
 Hinton, J. W., 391  
 Hirschboeck, J. S., 250  
 Hirschman, A., 106  
 Hisaw, F. L., 548  
 Hiscow, H. B., 14  
 Hitchcock, C. R., 79, 90  
 Hitchcock, F. A., 120, 190, 191, 192, 266  
 Hitchings, G. H., 82  
 Hjermsman, H. A., 542  
 Hjorth, E., 247  
 Ho, T. J., 29

- Hoagland, H., 422, 427, 432, 445  
 Höber, R., 399  
 Hoberman, H. D., 88, 515  
 Hochberg, I., 437  
 Hoch-Ligeti, C., 513  
 Hodes, R., 181, 457  
 Hodgkin, A. F., 399, 400, 401  
 Hodgkin, A. L., 399, 400, 402, 403  
 Hodge, H. C., 105  
 Hodge, M., 275  
 Hoelzel, F., 228  
 Hoff, E. C., 179, 314, 429, 448  
 Hoff, H. E., 181, 210, 216, 229, 457, 460  
 Hoffman, E., 131, 319  
 Hoffman, F., 131, 319  
 Hoffman, M. M., 157  
 Hoffmann, C. E., 79  
 Hoffmann, E. J., 295  
 Hoffmann, F., 295  
 Höfler, K., 17  
 Högberg, B., 508  
 Hogeboom, G. H., 17, 18, 19, 305, 307  
 Hogeman, O., 390  
 Hokin, L. E., 208  
 Holbrook, A. A., 192  
 Holden, H. F., 267  
 Holden, W. D., 33, 193, 249, 253, 326  
 Holder, M., 269  
 Hollaender, A., 31  
 Holland, B. C., 272, 322  
 Holland, H., 246  
 Hollander, F., 215, 221  
 Hollander, V., 150, 153  
 Hollinshead, W. H., 504  
 Holm, B., 215, 218  
 Holman, R. L., 386  
 Holmes, J. H., 154, 159, 168, 381  
 Holmstedt, B., 332  
 Holt, G. W., 191  
 Holt, J. F., 213  
 Holtfreter, J., 17  
 Holtkamp, D. E., 519  
 Holton, P., 221, 330  
 Holtz, F., 106  
 Hotyoke, E. A., 546  
 Homburger, E., 271  
 Homburger, F., 514  
 Honck, C. R., 377  
 Honorato, R., 241, 242, 244, 246, 255  
 Hoobler, S. W., 192, 213, 316, 323, 331, 459  
 Hooker, C. W., 546, 547  
 Hopkins, H. S., 399  
 Hoppe, J. D., 229  
 Horanyl, M., 254  
 Horger, E. L., 192, 359  
 Horn, Z., 252  
 Horne, H. W., Jr., 451  
 Horner, R., 193  
 Horowitz, N. H., 50, 54, 57  
 Horsten, G. P. M., 432, 437  
 Horton, B. T., 331, 332  
 Horvath, S. M., 121, 123, 124, 128, 316, 320, 321, 459  
 Horwitz, O., 279  
 Horwitz, S. A., 184, 266  
 Hotchkiss, R. D., 305  
 Hottinguer, H., 62  
 Houck, C. R., 151  
 Houdart, R., 434  
 Houet, R., 107, 108  
 Houlahan, M. B., 48, 50, 54, 55, 56  
 Houston, C. S., 192, 275  
 Houston, R. A., 489  
 Howard, E., 513  
 Howard, F. A., 193  
 Howarth, F., 29  
 Howarth, S., 320, 350  
 Howat, H. T., 212  
 Howell, W. L., 181  
 Hsü, E. H., 476  
 Hubbell, D. S., 357  
 Huber, G. C., 373  
 Huble, J., 521  
 Huddleston, B., 522  
 Hudyma, G. M., 505  
 Huebner, W., 269  
 Huff, J. W., 81  
 Huggett, A. St. G., 87, 322  
 Huggins, C., 92  
 Huggins, R. A., 357  
 Hugh-Jones, P., 180  
 Hughes, A. F., 16  
 Hughes, D. E., 80  
 Hughes, E. C., 544  
 Hughes, H. A., 29  
 Hughes, W. F., Jr., 39  
 Huizinga, E., 179, 192  
 Hult, L., 102  
 Hultin, T., 22  
 Humble, J. G., 237  
 Humphrey, G. F., 540  
 Humphrey, J. H., 385  
 Humphreys, E. M., 39, 295  
 Humphreys, G. H., 185  
 Hunt, A. D., Jr., 157  
 Hunt, C. C., 356  
 Hunt, J. N., 212, 214  
 Hunter, F. E., Jr., 299  
 Hunter, F. R., 13  
 Hunter, J., 437  
 Hunter, J. A., 120, 192  
 Hunter, R. B., 38  
 Hunter, S. W., 79, 90, 275  
 Hurn, M., 243, 244, 245  
 Hursh, J. B., 401  
 Hurtado, A., 187, 275  
 Hurxthal, L. M., 509  
 Hutchinson, G. E., 422  
 Hutner, S. H., 79  
 Hutt, B. K., 121, 128  
 Huxley, A. F., 399, 400  
 Hwang, K., 222  
 Hyde, J., 431  
 Hyden, H., 437  
 Hyman, A., 363  
 Hyman, C., 189
- I**
- Iannucci, J. F., 154  
 Iglauer, A., 316, 355  
 Iliff, C. E., 39  
 Imig, C. J., 540  
 Inatome, M., 278  
 Inberg, K. R., 459  
 Ingelfinger, F. J., 272  
 Ingersoll, H. G., 23  
 Ingle, D. J., 86, 108, 157, 380, 509, 513, 515, 518, 519  
 Ingraham, R. C., 378  
 Ingram, W. R., 433  
 Innes, I. R., 314  
 Inouye, T., 140  
 Irving, J. I., 107, 108  
 Irving, J. T., 106  
 Irving, L., 279  
 Irwin, E. A., 47  
 Irwin, H. R., 351  
 Issekutz, B., Jr., 192, 526  
 Itano, H. A., 268  
 Ivanoff, A., 498  
 Ivanovic, N., 241  
 Ivy, A. C., 191, 192, 205, 206, 209, 210, 211, 212, 214, 215, 217, 218, 221, 222, 226, 227, 274, 276  
 Ivy, J. H., 277
- J**
- Jackson, F. S., 192  
 Jacob, J., 193

# AUTHOR INDEX

571

Jacobs, J., 182, 436  
 Jacobs, W., 333  
 Jacobsen, C. F., 428  
 Jacobson, L. O., 32, 33, 253  
 Jacoby, J. J., 191  
 Jacox, H. W., 34  
 Jacox, R. F., 243  
 Jager, B. V., 157  
 Jahan, I., 529  
 Jailer, J. W., 505, 508, 546, 547  
 Jakus, M. A., 10  
 Jalavisto, E., 315, 318, 330  
 James, D. F., 246  
 James, G. A., 245  
 Jandorf, B. J., 303  
 Janowitz, H. D., 205, 206, 220, 449, 460, 477  
 Janzen, R., 426  
 Jaques, L. B., 246, 251, 252, 253  
 Jarisch, A., 314, 354, 454  
 Jarvis, J. L., 38  
 Jasper, H. H., 431  
 Jaynes, J., 428  
 Jeener, R., 11, 15, 19  
 Jeffers, W. A., 271, 320, 321, 459  
 Jefferson, G., 422  
 Jefferson, N. C., 227  
 Jeffries, J. W., 519  
 Jenkins, J. A., 53  
 Jennings, A. J., 542  
 Jensen, D., 246  
 Jensen, E. V., 92  
 Jensen, R., 252  
 Jensen, V., 208  
 Jerome, E. A., 476  
 Jeung, N., 12, 13  
 Jimenez Diaz, C., 333  
 Joekes, A. M., 391  
 Jögi, P., 209, 448  
 Johnson, A. A., 23  
 Johnson, A. C., 314  
 Johnson, A. D., 163  
 Johnson, B. J., 155  
 Johnson, H. C., 432  
 Johnson, J. R., 279  
 Johnson, L., 157  
 Johnson, M. N., 185  
 Johnson, P. L., 104  
 Johnson, R. E., 105, 124  
 Johnson, R. P., 360  
 Johnston, F. D., 361  
 Johnston, M. W., 155, 520, 526  
 Jones, A., 363  
 Jones, C. H., 428

Jones, D. C., 40  
 Jones, F. A., *see* Avery  
 Jones, F.  
 Jones, H. B., 79, 90, 105  
 Jones, I. C., 510, 549  
 Jones, P. H., *see* Hugh-Jones, P.  
 Jones, R. E., 311  
 Jones, R. N., 546  
 Jonxis, J. A. P., 270  
 Jope, H. M., 267  
 Jordon, M. L., 34  
 Jorpes, J. E., 252  
 Joseph, N. R., 103  
 Josephson, B., 370, 371  
 Jourdan, E., 320  
 Jourdan, F., 456, 459, 460  
 Jowsey, J. R., 105  
 Jubelirer, R. A., 255  
 Judd, D. B., 497  
 Judson, W. E., 157  
 Jukes, T. H., 79  
 Jungch, E. C., 549  
 Jürgens, R., 246, 248

## K

Kaada, B. R., 181, 429, 430, 447  
 Kadish, A. H., 255  
 Kaempfer, F., 320  
 Kahane, E., 452  
 Kahler, H., 19  
 Kahlson, G., 210, 459  
 Kahn, R. H. B., *see* Broh-Kahn, R. H.  
 Kaindl, F., 455, 457  
 Kaiser, I. H., 543, 544  
 Kalk, H., 378  
 Kaller, H., 292  
 Kallman, F., 18  
 Kaltreider, N. L., 180  
 Kaltus, A., 163, 164  
 Kaplan, N. O., 299  
 Kaplan, W. D., 48  
 Kappert, A., 389  
 Kar, A. B., 548  
 Karandikar, G., 526  
 Karel, L., 226, 227, 278  
 Kark, R. M., 124  
 Karp, D., 210  
 Karpe, G., 485, 494, 495  
 Kartin, B., 129  
 Kasdon, S. C., 542  
 Kassel, R., 18, 19  
 Katsh, S., 511  
 Katz, B., 399, 400, 401, 402  
 Katz, L. N., 189, 192, 193,

329, 351, 355, 359, 360, 361  
 Kaufman, P., 108  
 Kaufman, W., 362  
 Kaufmann, B. P., 48  
 Kaulbersz, J., 211, 212  
 Kaulla, K. N. v., 246  
 Kay, C. F., 312, 352  
 Kayden, H. J., 356  
 Kayser, C., 450  
 Kazal, L. A., 253  
 Kean, B. H., 313  
 Keating, R. P., 164, 323  
 Keegan, J. J., 437  
 Keele, K. D., 352  
 Keeton, R. W., 140, 294, 298  
 Kehl, R., 542, 547  
 Kehoe, R. A., 190  
 Keighley, G., 72, 75, 77  
 Keitt, G. W., 53  
 Kell, J. F., Jr., 314, 448  
 Keller, A. D., 133, 435, 449  
 Kelley, M. G., 19  
 Kelley, V. C., 192, 379  
 Kellogg, W. N., 436  
 Kelly, C. F., 297  
 Kelly, F. J., 326  
 Kemberling, S. R., 435  
 Kemp, C. R., 131  
 Kempf, J. P., 190  
 Kenawy, M. R., 358  
 Kendall, E. C., 516, 517  
 Kennedy, E. P., 19, 305, 306, 307  
 Kennedy, T. J., Jr., 371, 372  
 Kenney, J. F., 153  
 Kenney, R. A., 373  
 Kensler, C. J., 91  
 Kergin, F. G., 192  
 Kern, F., 225  
 Kerpel-Fronius, E., 153  
 Kerschman, J., 450  
 Kerslake, D. M., 131, 312, 318, 319, 355  
 Kester, W. O., 30  
 Keston, A. S., 74  
 Kety, S. S., 192, 271, 272, 317, 320, 321, 429, 549  
 Keutmann, E. H., 384  
 Keyes, P. H., 511  
 Keynes, R. D., 399  
 Keys, A., 153, 291, 322, 374, 456  
 Kibler, H. H., 292, 297  
 Kidder, G. W., 79, 92  
 Kiese, M., 269  
 Kihlmann, B., 48

- Kilian, D. J., 192, 279  
 Killick, E. M., 192, 273  
 Kilpatrick, J. A., 332  
 Kim, K. S., 218, 220  
 Kimball, R. F., 66  
 Kimeldorf, D. J., 40, 548  
 Kimmelstiel, P., 384  
 King, A. L., 179  
 King, B. D., 320, 321, 459  
 King, B. G., 274  
 King, E. J., 267, 268  
 King, F. H., 363  
 King, J. E., 541  
 King, R. B., 433, 435  
 Kinney, J. D., 323  
 Kinney, T. D., 184, 346, 348  
 Kinney, V. M., 276  
 Kinsell, L. W., 86, 509  
 Kinsey, D., 352, 453  
 Kirk, E., 228  
 Kirschbaum, A., 511  
 Kirsner, J. B., 39, 212, 213, 219  
 Kisch, B., 363  
 Kissin, M., 358  
 Kistin, A. D., 356  
 Kitching, J. A., 14  
 Kitzinger, C., 119, 120  
 Kjems, H., 253  
 Kleiber, M., 290, 296  
 Klein, R., 431  
 Klein, S., 522  
 Kleinschmidt, K., 192  
 Kleitman, N., 424, 450, 541  
 Kline, D. L., 329, 515  
 Kline, R. F., 192, 274  
 Klingelhöffer, K. O., 268  
 Klinghoffer, K. A., 165  
 Kloehn, N. W., 470  
 Klyne, W., 546  
 Knight, W. A., Jr., 221  
 Knight, W. R., 547  
 Knighton, R. S., 433  
 Knoefel, P. K., 223  
 Knott, J. R., 432, 433, 434, 448  
 Knowlton, N. P., Jr., 37, 39  
 Knox, J. A. C., 355  
 Knutson, J., 192, 267, 278, 279, 348  
 Kobayashi, Y., 82  
 Koch, A. C. E., 327  
 Kochakian, C. D., 509, 516  
 Kodama, S., 512  
 Kodicek, E., 107  
 Koella, W., 449, 459  
 Koelle, E. S., 171  
 Koelle, G. B., 357  
 Koenig, H., 193  
 Koenig, R., 193  
 Koerner, A., 546  
 Koets, P., 37  
 Kohn, H. I., 34, 39  
 Kölbel, H., 9  
 Koletsky, S., 380  
 Kolinsky, M., 322  
 Koller, F., 243, 252  
 Koller, P. C., 48  
 Kollos, J. J., 154, 171  
 Komarov, S. A., 215, 216, 223, 460  
 Konarev, V. G., 9  
 Koneff, A. A., 86  
 Konzett, H., 330, 352  
 Koopman, L. J., 432  
 Kopac, M. J., 10, 15, 17, 18, 19, 22  
 Kopeloff, N., 431, 433  
 Kornberg, A., 303  
 Koser, S. A., 71  
 Kosman, A. J., 316  
 Kossman, C. E., 278  
 Kostashuk, S. S., 311  
 Kosterlitz, H. W., 314  
 Kottke, F. J., 138, 188, 189, 191, 389  
 Kovach, S., 153  
 Krah, M. E., 521  
 Kraitz, L., 447  
 Krakusin, J., 166  
 Kramer, B., 106, 107  
 Kramer, H., 277  
 Kramer, K., 271, 317, 320, 330, 459  
 Krantz, J. C., 357  
 Kraus, A. P., 246  
 Kraus, S. D., 215  
 Krauss, M., 545  
 Krayner, O., 347  
 Krebs, H. A., 77, 79, 80, 148  
 Krehbiel, R. H., 544  
 Kremen, A. J., 79, 90  
 Krenz, F. H., 31  
 Kreps, E. M., 269  
 Krichesky, B., 548  
 Krichin, D. G., 278  
 Krieg, W. J. S., 433, 473  
 Krieger, H., 326  
 Krinsky, I., 304  
 Kriss, J. P., 333, 384  
 Kriszat, G., 486  
 Krogh, A., 120, 125  
 Kroner, T. D., 73  
 Krueger, H., 224  
 Krugelis, E. J., 11  
 Kruse, I., 247  
 Kruse, T. K. T., 327  
 Kruyt, W., 270  
 Kubicek, W. G., 188, 191, 389  
 Kubik, M., 246  
 Kuffler, S. W., 399  
 Kunde, M. M., 290  
 Kunkel, H. G., 166  
 Kuntz, A., 460, 461  
 Kupperman, H. S., 528, 549  
 Kurshakov, N. A., 278  
 Kuzell, W. C., 37  
 Kydd, G. H., 266

## L

- Labate, J. S., 246  
 LaBelle, C. W., 192  
 Labour, F. E., 192, 346  
 LaBrosse, E., 191  
 Lackey, M., 19  
 Lacroix, P., 101, 102  
 Ladell, W. S. S., 127, 155, 169  
 La Forge, M., 357  
 Lagerlof, H., 277, 346, 349, 350  
 Laker, D. J., 389  
 Laki, L., 254  
 Lalich, J. J., 380  
 Lalley, J. S., 252, 253  
 Lam, C. R., 192, 278  
 Lamas, A., 101  
 Lamb, M. W., 293  
 Lambert, E. H., 294, 298, 311  
 Lambertson, C. J., 183, 266, 267  
 Lambie, C. G., 193, 266  
 LaMer, V. K., 192  
 Lamport, H., 191, 312  
 Landahl, H. D., 192  
 Landauer, W., 109  
 Landis, E. M., 229, 312, 449  
 Landmesser, C. M., 271, 272  
 Landon, P., 274  
 Landowne, M., 318, 334  
 Landwehr, G., 243  
 Lane, A., 223, 350, 460  
 Lane, R. L., 220  
 Lang, L. P., 180, 189, 192  
 Lange, K., 272  
 Langston, M., 399

- Lantuejoul, P., 192  
 Lapique, L., 405  
 Laplaud, M., 538, 542  
 Laporte, Y., 452  
 Lapp, R. E., 29  
 Lardy, H. A., 539  
 Larinow, L. T., 7  
 Larnier, J., 303  
 Larrabee, M. G., 181, 452, 457  
 Larsen, W. E., 86, 509  
 Larson, F. C., 79  
 Lashley, K. S., 481  
 Lasichak, A. G., 228  
 Laskin, S., 192  
 Lassek, A. M., 426  
 Laszt, L., 323  
 Latarjet, R., 48, 62  
 Latterell, K. E., 193  
 Laufman, H., 237  
 Laughnan, J. R., 51, 52  
 Laundrie, B., 508, 521  
 Lauson, H. D., 166, 334, 350  
 Lawrence, J. H., 27, 105, 192, 273, 278  
 Lawrence, J. S., 34, 35, 248  
 Lawrence, W. J., 269  
 Lawson, F., 192  
 Lawson, H. C., 269  
 Lawson, H. D., 388  
 Lawton, R. W., 179  
 Lazarow, A., 519, 520  
 Lazarus, S., 324  
 Lea, D. E., 31  
 Leard, S. E., 192  
 Leatham, J. H., 510  
 Le Beau, J., 428, 434  
 Leben, C., 53  
 Leblond, C. P., 517, 526, 527, 528  
 Le Brun, E., 348  
 Lecomte, J., 34  
 Lecoq, R., 106, 107  
 Locrone, B. L., 228  
 Lederberg, E., 59  
 Lederberg, E. Z., 53  
 Lederberg, J., 47, 49, 50, 58, 59  
 Lee, A. J., 432, 433  
 Lee, C. C., 105  
 Lee, D. H. K., 127, 297, 298  
 Lee, G., 193  
 Lee, J. L., 40  
 Lee, J. M., 302  
 Leek, J. H., 111  
 Lefevre, P. G., 13, 545  
 Lefort, M., 30  
 Leger, J., 519  
 le Grand, Y., 496, 498  
 LeGros Clark, W. E., *see* Clark, W. E. LeG.  
 Lehmann, F. E., 19  
 Lehmann, G., 214  
 Lehniger, A. L., 19, 299, 305, 306, 307  
 Leibowitz, S., 358  
 Leicester, H. M., 101  
 Lein, A., 276  
 Lein, J., 48, 50, 54, 245, 249  
 Lein, P. S., 245, 249  
 Leitch, J. L., 37  
 Leiter, D. E., 161  
 Leiter, E., 357  
 Leiter, L., 161, 162, 163, 164, 375, 386  
 Leith, W., 519  
 Le Magnen, J., 476  
 Lemaire, R., 182, 193, 270, 322, 329, 458  
 Lempert, H., 245  
 Lenggenghager, K., 279  
 Lennox, E., 30  
 Lennox, W. G., 432  
 Leonard, C. S., 215  
 Leopold, I. H., 108, 271, 320, 321  
 Leopold, I. S., 108  
 Le Page, G. A., 306, 307  
 Lepp, E., 246  
 Lerman, L. S., 312  
 Lerner, A. B., 307  
 Leroy, G. V., 358  
 Lesbouyries, G., 551  
 Leslie, I., 19  
 Leslie, S. H., 156  
 Lesser, A. J., 525  
 Lesser, G., 193  
 Lester, D., 193  
 Leuchtenberger, C., 10  
 Leuret, J., 109  
 Leusen, I., 314  
 Leutscher, J. A., Jr., 166  
 Levan, A., 48  
 Levander, G., 102  
 LeVeen, H. H., 153  
 Levendahl, B. H., 88  
 Levey, S., 228  
 Levi, H., 12, 147  
 Levin, E., 212, 213, 219  
 Levin, L., 508, 515  
 Levin, W. C., 390  
 Levine, H. D., 362, 363  
 Levine, R., 227, 322, 522, 523  
 Levinson, L., 192  
 Levitt, J., 14  
 Levitt, M. F., 151  
 Levy, B. B., 150  
 Levy, B. M., 107  
 Levy, H. A., 29  
 Levy, I., 476  
 Lévy, J., 452  
 Levy, L., 192  
 Levy, L. K., 324  
 Lew, W., 229  
 Lewey, F. H., 475  
 Lewis, D., 52  
 Lewis, D. R., 470  
 Lewis, H. D., 269  
 Lewis, J. H., 242, 249  
 Lewis, L. A., 518, 519  
 Lewis, N. D. C., 428  
 Lewis, R. B., 192  
 Lewis, R. W., 56  
 Lewitus, Z. A., 246  
 Leyton, G., 249  
 L'Héritier, P. L., 62  
 Li, C. H., 57, 86, 87, 92, 101, 108, 109, 508, 509, 515, 516, 528, 549  
 Li, Mao-C., 131, 319  
 Lian, C., 453  
 Lian, T. Y., 88  
 Libet, B., 128, 319  
 Lichstein, H. C., 77  
 Lichtenstein, P. E., 470  
 Liddle, G. W., 271  
 Lieberman, S., 546  
 Liebow, I. M., 361  
 Lief, P. A., 356  
 Liegeois, F., 109  
 Ligeti, C. H., *see* Hoch-Ligeti, C.  
 Likely, G. D., 85  
 Lilienthal, J. L., Jr., 193, 253, 265, 267  
 Liljestrand, G., 184, 458  
 Lillehei, C. W., 217  
 Lillie, R., 437  
 Lin, C. Y., 223  
 Lindberg, O., 11, 303  
 Lindeboom, G. A., 385  
 Lindgren, C. C., 47, 52, 62  
 Lindenbaum, A., 106  
 Lindgren, I., 279  
 Lindsley, D. B., 435  
 Lindström, B., 11  
 Ling, W. S. M., 153  
 Linzbach, A. J., 352  
 Lipkin, D., 7  
 Lipmann, F., 75, 299  
 Lippman, R. W., 373

Lippold, O. C. J., 353  
 Lipton, B., 192  
 Lit, A., 499  
 Litter, J., 352  
 Little, C. C., 47  
 Little, J. M., 158, 213, 390  
 Little, R. C., 347  
 Little, W. J., 192, 316, 323, 331, 459  
 Lium, R., 221  
 Livermore, G. R., 212, 213  
 Livingston, K. E., 314, 429, 447  
 Livingston, R. B., 134, 314, 428, 429, 447  
 Livingston, W. K., 422  
 Livingstone, H. M., 191, 278  
 Lloyd, B. J., 19  
 Lloyd, C. W., 511  
 Lloyd, D. P. C., 401, 408, 409, 412, 415, 416  
 Lloyd, V. V., 499  
 Localio, S. A., 391  
 Lockard, I., 424  
 Lockwood, J. S., 193  
 Loeschke, G., 192, 271  
 Loeschke, H. H., 192, 271  
 Loew, E. R., 193  
 Loewe, L., 251  
 Löfström, B., 9  
 Loftfield, R. B., 72, 73, 75  
 Logan, M., 277  
 Logan, M. A., 73  
 Logan, V. W., 211  
 Loman, J., 271  
 Lombard, C. F., 181  
 Lombard, P., 104  
 Lo Monaco-Croce, T., 181  
 London, I. M., 76, 268  
 Long, C. N. H., 87, 88, 507, 513  
 Long, J., 193  
 Long, J. H., 184, 356  
 Longino, F. H., 223  
 Longmuir, N. M., 207, 208  
 Longwell, B. B., 519, 551  
 Loomis, E. C., 255  
 Loomis, T., 224  
 Looney, W. B., 30  
 Lopetegui, M., 246  
 Lopez, M. B. R., 391  
 Lorand, L., 254  
 Lorber, S. H., 216, 222, 223, 460

Lorber, V., 299  
 Lorch, I. J., 102, 103  
 Lord, M. P., 492  
 Lorente de N6, R., 399, 401, 402, 403, 404, 406, 409, 414, 416, 417, 452, 480  
 Lorenz, E., 36  
 Lorincz, A. L., 191  
 Loring, H. S., 56  
 Lotfield, R. B., 90  
 Lotspeich, W. D., 158, 371, 523  
 Lottenbach, K., 279  
 Louckes, H., 223, 460  
 Loucks, W. W., 311  
 Loufe, S. D., 522  
 Louis, L. H., 155, 520  
 Louis, P., 385  
 Loutit, J. F., 326  
 Love, L., 121, 128, 319  
 Love, L. H., 139  
 Low-Beer, B. V. A., 33  
 Lowe, T. E., 346, 352  
 Lowell, A., 166  
 Lowell, F. C., 192  
 Lowman, F. G., 32, 33  
 Lowy, P. H., 72, 75, 77  
 Loyd, C. W., 544  
 Lozner, E. L., 275  
 Lubin, M., 272, 359  
 Lubin, S., 543  
 Luck, J. M., 92  
 Lucké, B., 379  
 Luco, J. V., 456  
 Ludford, R. J., 7  
 Ludwig, C., 469, 478  
 Lueth, H. C., 30  
 Luft, U. C., 330  
 Lukens, F. D., 222  
 Lukens, R. M., 29  
 Lumio, J. S., 192  
 Lund, M., 386  
 Lundbaek, K., 294, 449  
 Lundberg, A., 399  
 Lundberg, W., 213  
 Lundholm, L., 193  
 Lundin, G., 183, 276  
 Lundy, J. S., 193  
 Luria, S. E., 62  
 Lusk, G., 290  
 Lutwak-Mann, C., 540  
 Lyman, C. P., 122  
 Lyons, C., 326, 327  
 Lyons, R. H., 213  
 Lyons, R. N., 254  
 Lyons, S. S., 191  
 Lyons, W. R., 549

Lyster, S. C., 218  
 Lythgoe, R. J., 489

## M

Maaske, C. A., 348  
 Maass, A. R., 79  
 Macallum, A. B., 524  
 McAlphine, H. T., 157  
 McBride, T. J., 249  
 McCabe, M., 332, 384  
 McCall, M. L., 321  
 McCance, R. A., 160  
 McCann, J. C., 193  
 McCann, S. M., 334  
 McCarter, J. C., 435  
 McChesney, E. W., 109  
 McCleary, B., 105  
 McClellan, W. S., 192  
 McClement, P., 29  
 McCormick, H. M., 246  
 McCorriston, J. R., 217  
 McCracken, W. J., 192  
 McCrory, W. W., 157  
 McCulloch, W. S., 422, 428, 431, 434, 449  
 McCullough, R. P., 324  
 McCune, D. J., 166, 385  
 MacCutcheon, F. H., 270  
 McDonald, D. A., 322  
 McDonald, I. W., 227  
 McDonald, M. R., 111  
 McDonald, R. K., 192, 379  
 McDowall, J. S., 192  
 McDowall, R. J. S., 312  
 MacDowell, M. C., 380  
 MacDuffee, R. C., 20  
 McEachern, D., 188, 527  
 Macey, R., 399  
 McFarland, R. A., 273  
 Macfarlane, R. G., 245, 254, 256, 268  
 McFie, J. M., 315  
 McGinty, D. A., 218, 528  
 Macgregor, W., 542  
 McGuire, J., 316, 355  
 MacGuire, W. B., Jr., 165  
 Mach, R. S., 107, 108  
 Machella, T. E., 216, 222  
 Machle, W., 296, 297  
 Macht, D. I., 253, 544  
 Macht, M. B., 125, 130, 133, 318, 332  
 McIlwain, H., 80, 83  
 MacIntosh, F. C., 452  
 McIntyre, A. K., 401, 416  
 McIntyre, D. B., 104  
 MacIntyre, W. H., 104

- Mackay, A. G., 218  
 McKay, E. A., 332  
 Mackay, R. S., 180  
 McKee, F. W., 166, 268  
 McKeen, C. L., 253  
 McKelvie, A. M., 103  
 MacKenzie, D. W., 217  
 MacKey, J., 48  
 McKinley, W. A., 480  
 MacKinney, G., 53  
 Mackler, B., 159  
 McLain, P. L., 326, 327  
 McLardy, T., 432, 447, 449  
 McLean, F. C., 103, 547  
 MacLeod, G., 293  
 McMichael, J., 161, 320, 350  
 McMichael, M., 189, 275  
 MacMillan, R. L., 245  
 McNamara, B. P., 171  
 McNamara, H., 151, 152, 171, 369, 370  
 McNamara, W. J., 109  
 MacNider, W. M. de B., 385  
 McNutt, S. H., 544  
 Macpherson, R. K., 127  
 McQuarrie, I., 145  
 McQuillan, M. T., 506  
 McShan, W. H., 549  
 Maculla, E. S., 17  
 Maddock, C. L., 246  
 Maddock, S., 221  
 Maddy, K. H., 81  
 Madinaveitia, J., 354  
 Madison, F. W., 251  
 Maffre, S., 323, 436, 458  
 Magath, T. B., 243  
 Magee, D. F., 218  
 Magee, H. E., 313  
 Magoun, H. W., 434, 435, 480  
 Maher, F. T., 223  
 Maher, P. J., 279  
 Mahoney, C. G., deG., *see* deGutierrez-Mahoney, C. G.  
 Mahoney, D. I., 190  
 Maier, C., 277  
 Main, E., 373  
 Mains, M. P., 38  
 Maison, G., 123, 193  
 Makarova, E. I., 269  
 Makarovskaya, Ts. D., 278  
 Malcolm, J., 529  
 Malcolm, J. L., 407, 417, 437, 455  
 Malméjac, J., 316, 330, 379, 451, 530  
 Malmström, G., 192, 265  
 Malone, P. D., 471  
 Maloney, J. V., 191, 455  
 Malorny, G., 186  
 Malpress, F. H., 546  
 Malton, D., 356  
 Maluf, M. S. R., 391  
 Mangieri, C. N., 253  
 Manhoff, L. J., 217  
 Mankin, H., 166  
 Mann, C. L., *see* Lutwak-Mann, C.  
 Mann, F. C., 103, 224, 228  
 Mann, F. D., 243, 244, 245, 247  
 Mann, J. D., 247  
 Mann, T., 539, 540  
 Mann, W. B., 193  
 Manning, G. W., 358  
 Marbarger, J. P., 190, 275  
 Marburg, O., 430  
 Marcenac, N., 544  
 Marchall, H. L., 104  
 Maresch, M. M., 351  
 Mark, L. C., 356  
 Markee, J. E., 449, 504, 543, 544  
 Marks, E. K., 33, 253  
 Markus, G., 279  
 Marois, M., 323  
 Marquis, H. H., 391  
 Marrazzi, A. S., 406, 452  
 Marrian, G. F., 546  
 Marsh, D. F., 311, 313, 329, 379  
 Marshak, A., 14  
 Marshall, F. H. A., 537  
 Marshall, L. H., 154, 189, 275  
 Marshall, M. R., 331  
 Marshall, W. H., 431  
 Marsland, D., 22  
 Marston, H. R., 292  
 Martin, A. J. P., 72, 73  
 Martin, C. G., 191  
 Martin, E. E., 271, 279, 317  
 Martin, G. J., 246, 277  
 Martin, W. B., 237, 347  
 Martin-Bellet, F., 403  
 Martinet, M., 507  
 Marvin, H. M., 79, 311, 514  
 Maruyama, G. M., 550  
 Masmonteil, F., 109  
 Mason, H. L., 157, 548  
 Massie, E., 164  
 Masson, G., 329  
 Mateer, F. M., 171  
 Mather, K., 47  
 Mathis, A. L., 31  
 Mathis, J. C., 509  
 Matthes, K., 313, 317  
 Matthews, J. I., 549  
 Matthews, L. H., 541  
 Maury, P. B., *see* Bonet-Maury, P.  
 Mautz, F. R., 191  
 Mawson, C. A., 244  
 Maxwell, H., 271  
 Maxwell, M. H., 164  
 May, L. G., 350  
 Mayer, G., 547  
 Mayer, H., 376  
 Mayer, J., 80  
 Mayer, J. E., 146  
 Mayerson, H. S., 326, 327  
 Maynard, L. A., 101  
 Mazia, D., 21, 31  
 Mazoué, H., 106  
 Mazur, A., 329, 382  
 Mead, J., 130, 131, 318, 319  
 Mead, S., 182, 457  
 Means, J. H., 528  
 Mears, F. B., 216  
 Medawar, P. B., 67  
 Medem, F., 545  
 Medinets, H. E., 389  
 Meduna, L. J., 192  
 Meehan, J. P., 189, 328  
 Meek, W. J., 357  
 Meeter, E., 184  
 Meier, K., 108  
 Meier, K. G., *see* Gollwitzer-Meier, K.  
 Meier, R., 11, 279, 330, 349  
 Meigs, J. W., 192  
 Meites, J., 506, 549  
 Melchior, J. B., 73  
 Mellanby, E., 107  
 Mellgren, J., 507  
 Mellinger, G. W., 188  
 Melloni, G. F., 274  
 Melon, J., 101, 102, 103, 104, 110, 111  
 Melville, K. I., 357  
 Mendelson, D. J., 334  
 Mendelson, E. S., 128, 319  
 Mendlowitz, M., 313, 325  
 Menely, G. R., 180  
 Menendez, E. B., *see* Braun-Menendez, E.

- Menghini, G., 253  
 Mercker, H., 318  
 Meredith, W. J., 32  
 Merendino, K. A., 216  
 Merino, C. F., 187  
 Merlis, J. K., 432  
 Merrill, A. J., 161, 162, 164, 375  
 Mertens, O., 318  
 Meserve, E. R., 294  
 Messinger, W. J., 150  
 Mettler, F. A., 425, 427, 449  
 Metz, B., 192  
 Metz, C. B., 66  
 Metzger, N., 525  
 Meyer, A., 447  
 Meyer, K. A., 211, 213, 215, 216, 453  
 Meyer, K. H., 220  
 Meyer, M., 479  
 Meyer, R. K., 549  
 Meyers, R., 434, 448  
 Meyersburg, R., 49  
 Meyling, H. A., 454  
 Michaels, G. D., 86, 509  
 Michaelson, J. B., 525  
 Michelsen, O., 153  
 Michie, A., 334, 350, 388  
 Michie, C., 334, 350  
 Michie, K., 388  
 Middleton, S., 455, 456  
 Migicovsky, B. B., 106, 107, 108  
 Mihalvi, E., 252, 254  
 Miles, W. R., 477  
 Milham, H., 253  
 Milhet, M. F., 256  
 Milhorat, A. T., 291  
 Millen, H. M., 212  
 Millen, J. W., 316  
 Miller, A. H., 540  
 Miller, A. T., Jr., 510  
 Miller, B. J., 325  
 Miller, C. P., 60  
 Miller, D. C., 513  
 Miller, E., 36  
 Miller, E. B., 30  
 Miller, E. C., 19, 91  
 Miller, G. L., 318  
 Miller, G. M., 92  
 Miller, J. A., 19, 91  
 Miller, J. M., 193  
 Miller, J. R., 228  
 Miller, L. L., 77, 219  
 Miller, M. R., 541  
 Miller, N., 31  
 Miller, O. N., 299, 300  
 Miller, R. A., 274  
 Miller, R. N., 121  
 Miller, W. W., 73  
 Miller, Z. B., 103, 300, 304  
 Milstone, J. H., 238  
 Minckler, J., 322, 374  
 Minkowski, A., 160, 167  
 Minkowski, M., 449  
 Mintz, B., 545  
 Mirone, L., 550  
 Mirsky, A. E., 7, 10, 18, 19, 72  
 Mirsky, I. A., 214, 520, 521, 522, 523  
 Mita, T., 494, 495  
 Mitchell, G. A. G., 390  
 Mitchell, H. H., 294, 295, 298  
 Mitchell, H. K., 48, 49, 50, 53, 54, 55, 56  
 Mitchinson, A. G. H., 192  
 Mittler, A., 111  
 Moe, G. K., 193, 213, 312, 331, 356, 453  
 Moehlig, R. C., 109  
 Mohamed, M. S., 225  
 Mohney, J., 266  
 Moir, W. W., 39  
 Mokotoff, R., 162, 163, 164, 375  
 Molano, P. A., 193, 376  
 Mole, R. H., 139, 154, 254  
 Molina, A. F. de, *see* de Molina, A. F.  
 Molina, C., 542  
 Moncrieff, R. W., 469, 470, 477  
 Money, W. L., 548  
 Monge, C., 163, 164, 179  
 Monkhouse, F. C., 252, 253  
 Monné, L., 17, 21, 545  
 Monnier, A. M., 103, 404  
 Monnier, M., 432, 494, 495  
 Monroe, R. A., 527  
 Monroy, A., 15  
 Montgomery, G. E., 192, 278, 279  
 Montgomery, H., 279  
 Moody, J. D., 546  
 Moog, F., 102, 107  
 Moolten, S. E., 251  
 Moon, V. H., 378  
 Moore, C. R., 541  
 Moore, F. D., 150, 152  
 Moore, G. E., 79, 90  
 Moore, J. C., 269  
 Moore, L. A., 540  
 Moore, S., 72  
 Moore, T., 246  
 Morales, M. F., 278  
 Mörch, E. T., 385  
 Moreau, R. E., 540  
 Morel, F., 323  
 Morelli, H. E., 152  
 Morgan, A. F., 108  
 Morgan, B. B., 544  
 Morgan, D. P., 182  
 Morgan, G. W., 29  
 Morgan, K. Z., 29  
 Morgan, R., 189  
 Morin, G., 436, 461  
 Moring-Claesson, I., 74, 77  
 Morissette, R. A., 107  
 Moritt, E., 189  
 Morley, F. H. W., 541  
 Morlock, C. G., 212, 223  
 Morriane, T. P., 215  
 Morris, J. R., 297  
 Morris, R. E., 426  
 Morrison, J. L., 331  
 Morrison, M., 251  
 Morrison, P. R., 254, 292  
 Morrissey, M. J., 193, 266, 279, 349  
 Morse, A., 103  
 Morse, M., 152, 269, 313, 355  
 Morse, R. A., 357  
 Morse, W. I., 238, 244, 248  
 Morton, G. M., 209  
 Morton, R. A., 486, 487, 489  
 Moruzzi, G., 435, 436  
 Moschcowitz, E., 251, 385  
 Mosinger, M., 448  
 Moskowitz, M., 86  
 Mote, F. A., 499  
 Motley, H. L., 180, 189, 191, 192, 350  
 Motokawa, K., 494, 495, 500  
 Moulder, P. V., 253  
 Mountcastle, V. B., 430, 433, 446, 474  
 Movitt, E., 328  
 Moyer, J., 183, 267, 271  
 Mudd, S., 20  
 Mudge, G. H., 154, 164, 171, 371  
 Mueller, C. G., 499  
 Mueller, R. D., 499  
 Muether, R. D., 221  
 Muirhead, E. E., 251, 333  
 Mukherjee, R., 295

Mullens, L. J., 106  
 Müller, A., 312  
 Muller, H. J., 47  
 Mulligan, R. M., 108, 109, 185  
 Mully, K., 277  
 Mulryan, B. J., 39, 105  
 Munch-Petersen, A., 22  
 Munro, D., 451  
 Munro, F. L., 242  
 Munro, H. N., 324  
 Munro, M. P., 242  
 Muntz, J. A., 30, 147  
 Murlin, J. R., 295  
 Murphy, D. P., 37  
 Murphy, E. A., 73, 80, 91  
 Murphy, P., 214  
 Murphy, Q. R., 357  
 Murphy, R. C., 240, 241  
 Murray, G., 391  
 Murray, P. D., 101, 107  
 Murray, R., 32  
 Murray, R. V., 325  
 Mushett, C. W., 246  
 Muylder, C. de, *see de*  
 Muylder, C.  
 Myers, J. D., 272, 322  
 Myers, T. T., 324, 351  
 Myerson, A., 271  
 Mylon, E., 385, 386

## N

Nachmansohn, D., 399, 452  
 Nadler, C. S., 271  
 Nadlet, C. S., 320, 321  
 Nahum, L. H., 129, 362  
 Nalbandov, A. V., 549  
 Nalefski, L. A., 358  
 Nance, M. H., 241, 242, 246  
 Naranjo, A., 85  
 Nasset, E. S., 293, 295  
 Nastuk, W. L., 328  
 Naurais, E., 530  
 Neal, P. A., 192  
 Necheles, H., 220, 222, 227, 228  
 Needham, B. M., 313  
 Neher, B. H., 542  
 Neidle, E. A., 454  
 Neil, E., 314  
 Nelemans, F. A., 454  
 Neligh, R. B., 213  
 Nelson, L., 539  
 Nelson, M. M., 107, 550  
 Nelson, W. P., 157  
 Nemir, P., Jr., 228

Netsky, M. G., 447  
 Neuberger, A., 299  
 Neuman, M. W., 39, 105  
 Neuman, W. F., 39, 105  
 Neverre, G., 530  
 Neville, G. A., 37  
 Neville, J. F., Jr., 192, 278, 279  
 Newcombe, H. W., 59, 60  
 Newell, R. R., 28, 29  
 Newman, E. V., 163, 164  
 Newman, H. F., 541  
 Newton, M., 121, 124, 128, 167, 319, 327, 329  
 Nezamis, J. E., 86, 380, 513, 515, 518, 519  
 Nguyen-Van-Thoai, 103  
 Nicholas, C. H., 124  
 Nicholas, J. S., 545  
 Nichols, J., 188, 510, 519  
 Nickerson, J. L., 277, 311, 349  
 Nickerson, M., 334, 356, 453, 504, 543  
 Nickerson, W. J., 11  
 Nickson, J. J., 28, 29, 33  
 Nicola, P. de, *see de*  
 Nicola, P.  
 Nicoll, P. A., 323  
 Nieburgs, H. E., 544  
 Nielsen, B. S., *see*  
 Schmidt-Nielsen, B.  
 Nielsen, K. S., *see*  
 Schmidt-Nielsen, K.  
 Nielsen, M., 132, 136, 182, 276  
 Niemer, W. T., 435  
 Nienaber, M. W. P., 107  
 Nieset, R. T., 326  
 Nieuwmeijer, A. H., 313  
 Nikolaeva, N. I., 249  
 Nimmo-Smith, R. H., 184  
 Nims, L. F., 37, 129  
 Nisell, O., 323  
 Nitti, F. B., *see* Bovet-Nitti, F.  
 Niven, J. I., 273  
 Nizet, A., 327  
 Noback, C. R., 528  
 Noble, R. L., 514  
 Noble, R. P., 277  
 Noda, L., 92  
 Noell, W., 192, 271, 321  
 Noell, W. K., 186, 192  
 Nolan, J., 193, 279  
 Nolte, A., 9, 19  
 Nomaguchi, G. M., 334, 356  
 Noonan, T. R., 76

Norman, G. F., 111  
 Noro, L., 192, 274  
 Norris, C. M., 193  
 Norris, W. P., 29  
 North, N., 37  
 Northup, D. W., 187, 192, 223, 224  
 Norviit, L., 391  
 Nothman, M. M., 221  
 Nulsen, F., 453  
 Nyc, J. F., 53  
 Nye, W. N., 92  
 Nylin, G., 327

## O

Obel, N. J., 192  
 O'Brien, J. R. P., 267  
 O'Connor, R. J., 193  
 O'Connor, W. J., 381, 449  
 Odel, H. M., 391  
 Odell, L. O., 385  
 Oder, D. L., 540  
 Oderladi, E., 508  
 O'Doherty, K., 81, 295  
 Oehlkers, F., 48  
 Oesterling, M. J., 79  
 Ogden, E., 311, 325, 334, 352, 381  
 Ogle, B. C., 331, 390  
 Ohlsson, W. T. L., 276  
 O'Leary, J. L., 433  
 Olesen, J., 132  
 Olivecrona, H., 9  
 Oliver, J., 253, 372, 380  
 Oloufa, M. M., 539  
 Olsen, M. W., 542  
 Olsen, N. S., 333  
 Olsen, R. S., *see* Strom-Olsen, R.  
 Olson, R. E., 299, 300  
 Olwin, H. J., 245  
 O'Neil, J. B., 105  
 Ong, S. G., 192  
 Opdyke, D. F., 192, 347, 358  
 Opie, E. L., 13, 149  
 Opitz, E., 271, 277  
 Oppel, T. M., 130  
 Oppenheimer, M. J., 184, 193, 346, 349, 356  
 Opsahl, J. C., 518  
 Orahovats, P. D., 325  
 Ordway, N. K., 192, 267  
 Orgain, E. S., 334  
 Orloff, J., 165  
 Orsini, D., 292  
 Ortavant, R., 538, 542  
 Orth, O. S., 357

Osborn, C. M., 158  
 Osborn, S. B., 325  
 Oser, B. L., 107  
 Osher, S., 214  
 Oster, G., 21  
 Oster, J., 370  
 Osterhout, W. J. V., 146  
 Otero, J. M., 498  
 Otis, A. B., 180, 182, 186,  
 188, 190, 192, 266, 274,  
 275, 276, 277  
 Ould, C. L., 223  
 Overman, R. R., 153, 377  
 Overman, R. S., 249  
 Owen, C. A., 244  
 Owren, P. A., 242  
 Ozorio de Almeida, M.,  
 405

## P

Pace, J. M., 386  
 Pace, N., 266, 273, 275  
 Paff, G. H., 102  
 Page, I. H., 151, 238, 328,  
 329, 331, 332, 334, 383,  
 388, 389, 390, 453, 458,  
 518, 519  
 Paine, J. R., 278  
 Paine, R., 161, 193  
 Painter, E. E., 154, 168  
 Pallade, E. G., 17, 18, 19,  
 305  
 Pallares, D. S., *see* Sodi-  
 Pallares, D.  
 Palmer, A. J., 279, 349  
 Palmer, G., 104  
 Palmer, H. D., 226  
 Palmer, W. L., 39, 212,  
 213, 219  
 Palmes, E. D., 120, 121,  
 137, 139, 451  
 Palomera, E. S., *see* San-  
 chez-Palomera, E.  
 Pannier, R., 314  
 Panzorella, F. P., 550  
 Paolini, A., 225  
 Pappas, A., 77, 80  
 Pappenheimer, J. R., 320  
 Papper, E. M., 453  
 Parant, M., 107  
 Park, C. R., 120, 121, 137,  
 521  
 Park, H. W., 229, 312  
 Parker, R. L., 192, 278,  
 279  
 Parkinson G., B., 193  
 Parks, E. R., Jr., 79, 92  
 Parmington, S. L., 160

Parry, D. A., 490  
 Parry, T. M., 191, 277  
 Parson, W., 326, 327  
 Parsons, C. L., 346  
 Parsons, R. P., 30  
 Parsons-Smith, G., 431  
 Paschkis, K. E., 505, 528,  
 547  
 Pask, E. A., 191  
 Pasteels, J., 16  
 Paton, W. D. M., 190,  
 193, 279  
 Patras, M. C., 109  
 Patt, H. M., 37, 122  
 Patterson, M. C., 246  
 Patterson, T. L., 212  
 Patterson, W. B., 208  
 Patton H. D., 453, 471,  
 472, 473, 474, 475  
 Patton, T. B., 238  
 Patwardhan, V. N., 107  
 Pauker, R. S., 541  
 Paul, W., 192, 279  
 Paul, W. J., 81, 295  
 Paulett, J., 351  
 Pauling, L., 267, 268  
 Paull, D. P., 451  
 Payne, R. W., 509  
 Pearce, E. L., 81  
 Pearl, F. L., 331  
 Pearlman, W. H., 547  
 Pearce, H. E., 218  
 Pearson, A. A., 435  
 Pearson, O. P., 541  
 Peart, W. S., 330  
 Pease, D. C., 20  
 Peck, H. M., 193  
 Pecora, L. J., 266, 275  
 Pederson, L., 120  
 Peet, M. M., 316, 331  
 Peiss, C. N., 134  
 Pellmont, B., 279  
 Pendergrass, E. P., 37  
 Penfield, W., 424, 425,  
 427, 428, 430, 474, 475,  
 481  
 Pennes, H. H., 129, 317  
 Pennybacker, J., 39  
 Penneys, R., 266  
 Penrod, K. E., 123, 186,  
 190, 275, 276, 278, 279  
 Pentz, E. I., 513, 514, 515  
 Pequegnat, W. E., 545  
 Peralta, R. B., 193, 453  
 Perkins, J. F., 124, 131,  
 319  
 Permin, P. M., 255  
 Perlow, S., 246  
 Perlmutter, M., 521

Perrin, L., 252  
 Perry, C. H., 29  
 Perryman, J. H., 451  
 Peskin, J. C., 497  
 Peters, G. A., 331, 332  
 Peters, J. H., 148, 171  
 Peters, J. P., 155, 156, 158,  
 161, 162, 164, 166, 170  
 Petersen, A. M., *see*  
 Munch-Petersen, A.  
 Peterson, E. R., 159  
 Peterson, J. M., 267  
 Peterson, L. H., 128, 311,  
 314, 346, 350  
 Petrakis, N. L., 38  
 Pettengill, O., 12  
 Pfaffman, C., 469, 472,  
 473, 475  
 Pfeiffer, C. A., 102, 111  
 Pfeiffer, J. B., 388  
 Pfeiffer, J. P., 334  
 Phalen, J. S., 138, 189  
 Phillips, F. S., 171  
 Phillips, C. W., 227  
 Phillips, N. E., 189, 296  
 Phillips, P. H., 550  
 Phillips, R. A., 379, 380  
 Phillipson, A. T., 227  
 Phinney, B. O., 54  
 Pickels, E. G., 19  
 Pickering, G. W., 387  
 Pickering, R. W., 328  
 Pierce, J. G., 56  
 Pierce, M., 253  
 Pietrafesa, E. R., 192, 346  
 Pigón, A., 17  
 Pilhorn, H. R., 546  
 Pillion, E. L., 131  
 Pincus, G., 540, 546, 549  
 Pincus, J. B., 107  
 Pindborg, J. J., 111  
 Pines, K. L., 330, 352  
 Pino, J. A., 36  
 Pirenne, M. H., 485, 498  
 Pirie, N. W., 540  
 Pitts, G. C., 266, 273, 275  
 Pitts, R. F., 155, 371, 529  
 Pitts, W., 400, 404, 406,  
 422, 423  
 Platt, R., 333, 385  
 Plaza, L., 498  
 Pletcher, D. E., 477  
 Plotkin, T., 193  
 Podore, 214, 523  
 Poel, W. E., 192, 275  
 Pogrund, R. S., 190, 228  
 Pohle, E. A., 39  
 Pohle, F. J., 251  
 Poindexter, C. A., 357

Polis, B. D., 271, 320, 321  
 Pollack, A. A., 312, 324, 348, 351  
 Pollack, H. L., 8  
 Pollard, E. C., 31  
 Polley, H. F., 516, 517  
 Polley, J. R., 384, 388  
 Pollister, A. W., 10  
 Pollock, G. H., 192, 431  
 Pollock, L. J., 451  
 Polonowski, M., 105  
 Polyak, S. L., 491  
 Polzer, K., 455, 457  
 Pomper, S., 49  
 Pond, H. S., 192  
 Pons-Tortella, E., 383  
 Pontecorvo, G., 49, 61  
 Pontius, R. G., 182, 183, 193, 266, 267, 353, 458  
 Pool, J. L., 428, 447  
 Pootz, O., 430  
 Popper, H., 106, 226  
 Popper, H. L., 220, 222  
 Porter, B., 326, 327  
 Porter, K. R., 19, 20, 21, 23, 254  
 Portmann, A. F., 33, 249  
 Posey, E. L., Jr., 222, 224, 453  
 Post, R. L., 268, 328, 329  
 Posternak, J. M., 452  
 Postlethwait, R. W., 216  
 Poth, E. J., 217  
 Potter, J. M., 322  
 Potter, V. R., 306, 307  
 Poupa, O., 321  
 Powell, A. K., 9  
 Powell, N., 391  
 Power, M. H., 157, 190, 221, 275, 391  
 Powers, S., 272, 359  
 Praet, J. W., 186  
 Pratt, E. L., 154, 160, 170  
 Pratt, T. D., 221  
 Prec, O., 355, 359  
 Preer, J. R., 63, 64  
 Preisler, P. W., 299  
 Presnell, M. W., 161, 449  
 Preston, S. N., 192, 267  
 Prestud, M. C., 86, 515  
 Primbram, K. H., 181, 429, 430, 447, 448, 449  
 Price, C. H. G., 33  
 Price, D., 541  
 Price, F. L., 30  
 Price, J., 434  
 Price, J. M., 19, 91  
 Price, W. H., 86

Prichard, M. M. L., 373, 374, 378, 379, 382, 384  
 Priestly, J. T., 228  
 Prince, P. W., 539  
 Prince, R., 331, 453  
 Prinzmetal, M., 348, 383, 387  
 Pritchard, W. H., 346, 358, 458  
 Probst, J. M., 312  
 Proctor, B. E., 31  
 Proemmel, D. D., 265, 267  
 Prosser, C. L., 37  
 Prost, M., 519  
 Prouty, L. R., 120, 140, 289, 296  
 Provasoli, L., 79  
 Prudhomme, R. O., 18  
 Pruitt, R. D., 192, 359  
 Pruneyre, A., 323, 458  
 Prunty, F. T. G., 157, 510  
 Pruss, M., 193  
 Puck, T. T., 193  
 Pugsley, L. I., 546  
 Pulfrich, K., 317, 320  
 Pulver, R., 246  
 Pumprey, R. J., 423  
 Pye, O. F., 293

## Q

Quashnock, J. M., 148, 171  
 Quastel, J. H., 299  
 Quelch, P. E., 267  
 Quick, A. J., 238, 239, 241, 242, 243, 244, 245, 246, 247, 248, 250, 251, 252, 255  
 Quigley, J. P., 222, 223, 460  
 Quimby, F. H., 189, 296  
 Quin, J. I., 548  
 Quivy, D., 253

## R

Raab, D. H., 425  
 Rabinovitch, R., 188  
 Rachmilewitz, M., 268, 360  
 Racker, E., 304  
 Rader, B., 128  
 Radhakrishna, M. V. R., 247  
 Ragan, M. S., 550  
 Rahn, H., 180, 183, 186, 188, 190, 192, 266, 274, 275, 276, 277

Raimondi, P. J., 206, 476  
 Rakoff, A. E., 547  
 Rakshit, P., 184  
 Rall, D. P., 137  
 Ralli, E. P., 156, 513  
 Ralston, H., 220  
 Ramirez, H. P. R., *see* Redondo Ramirez, H. P.  
 Ramos, J. G., *see* Garcia Ramos, J.  
 Rampton, S. E., 546  
 Ramsay, W. N. M., 267, 269  
 Randak, E. F., 346  
 Randall, A., 247  
 Randall, J. P., 247  
 Randall, J. T., 21  
 Randall, S. S., 73  
 Randall, W. C., 130, 139, 297, 317  
 Ransohoff, J., 447  
 Rapaport, S. I., 125  
 Rapoport, A., 422  
 Rapoport, S., 159, 170, 334  
 Rappaport, M. B., 346, 361  
 Rapport, M. M., 238  
 Rashevsky, N., 400, 404  
 Rasmussen, T., 424, 425  
 Rathbun, H., 248  
 Rathbun, J. C., 148, 171  
 Rather, L. J., 380  
 Ratke, H. V., 212, 213  
 Ratner, S., 77, 80  
 Ratnoff, O. D., 255  
 Ratoosk, P., 499  
 Ratsimananga, A., 519  
 Rau, C. G., 329  
 Ravel, J. M., 79  
 Raventos, J., 354  
 Rawson, R. W., 524, 528  
 Ray, G. B., 279  
 Ray, L. H., 279  
 Reade, M. A., 105  
 Reader, R., 384  
 Reardon, M. J., 453  
 Reaser, P., 161  
 Redondo Ramirez, H. P., 181  
 Redwood, C. R. M., 314  
 Reed, B. P., 110  
 Reed, C. I., 108, 110, 323  
 Reed, E. A., 181, 182, 457  
 Reed, J., 429  
 Reed, J. C., 105  
 Reed, J. O., 506  
 Reese, J. W., 75  
 Reeve, E. B., 326

- Reeves, R. J., 324  
 Regdon, R. H., 270  
 Rehm, W. S., 207, 208  
 Reich, C., 251  
 Reid, E., 521  
 Reid, J. C., 79, 90  
 Reid, J. T., 550  
 Reifenstein, E. C., 110  
 Rein, F. H., 179  
 Rein, H., 272  
 Reinecke, R. M., 294, 380  
 Reineke, E. P., 528  
 Reinhard, E., 110  
 Reinhard, E. G., 545  
 Reinhard, J. J., 329, 331, 453  
 Reinis, Z., 246  
 Reiser, M. F., 334, 388  
 Reiss, M., 522  
 Reiss, R. A., 347  
 Reitman, F., 429, 447  
 Rekers, P. E., 34  
 Keller, E., 292  
 Reiman, A. S., 159, 331  
 Remington, J. W., 163, 277, 328, 345, 349, 379  
 Rémond, A., 192  
 Renard, C., 255  
 Renault, J., 106  
 Rennes, P., 476  
 Rennick, B., 347  
 Rennick, B. R., 331  
 Rennick, R., 356  
 Renshaw, B., 406, 417, 437, 457  
 Repela, C., 390  
 Reubi, F. C., 382  
 Rexed, B., 509  
 Reynafarje, C., 187  
 Reynolds, O. E., 187  
 Reynolds, S. R. M., 325, 543  
 Rhines, R., 435  
 Rhoads, C. P., 89, 546  
 Ribadeau-Dumas, L., 192  
 Richards, C. H., 120  
 Richards, D. W., 189, 277, 345  
 Richards, D. W., Jr., 161, 191, 192  
 Richardson, E., 333, 386, 387  
 Richins, C. A., 322, 460  
 Richter, C. P., 469, 470, 471, 472  
 Richter, I. H., 251  
 Ricker, A. G., 253  
 Ricketts, H. T., 192  
 Ricketts, W. E., 39, 219  
 Riddle, O., 111  
 Ridgway, A. M., 127, 291  
 Ridout, J. H., 520  
 Rieser, P., 8  
 Rigdon, R. H., 380  
 Riggs, L. A., 499  
 Rijlant, P., 181  
 Riley, R. F., 105  
 Riley, R. L., 183, 184, 265, 267, 275, 277, 348, 350  
 Riley, V. T., 18  
 Rinaldini, L. M., 506  
 Ring, G. C., 349  
 Rinzier, S., 358  
 Ripely, H. S., 334, 388  
 Ris, H., 7, 10, 16, 18, 19  
 Risman, G. C., 311, 346  
 Rittenberg, D., 76, 80, 268  
 Ritchie, G., 39  
 Rivera, A. S., *see* Soto-Rivera, A.  
 Robb, J. S., 362  
 Robbie, W. A., 16  
 Robbins, M. E., 134  
 Robelet, A., 322  
 Roberts, C., 62  
 Roberts, E., 73  
 Roberts, J. T., 357  
 Roberts, K., 158  
 Roberts, P. W., 193  
 Roberts, T. B., 422  
 Robertson, C. R., 209, 211, 213, 223, 460  
 Robertson, C. W., 312  
 Robertson, H. F., 192  
 Robertson, H. S., 451  
 Robertson, M. E., 293  
 Robin, I. G., 192  
 Robinett, P. W., 34  
 Robinson, C. S., 227  
 Robinson, F., 425  
 Robinson, F. B., 510  
 Robinson, J. E., Jr., 248  
 Robinson, J. N., 36  
 Robinson, S., 136  
 Robinson, T. W., 190  
 Roche, J., 102, 103  
 Rockland, L. B., 79, 80  
 Rodbard, S., 121, 128, 130, 134, 184, 189, 192, 193, 329, 348, 351, 355, 360, 433, 449  
 Rodney, G., 218  
 Rodwell, A. W., 78  
 Roeder, K. D., 452  
 Roemhild, F., 378  
 Roger, M., 103  
 Rogers, L. L., 82  
 Rogerson, A. G., 157  
 Roh, C. E., 185, 330  
 Rohlin, S., 192  
 Rojas, C., 241  
 Rokaw, S. N., 164  
 Rolf, D., 192, 295, 323, 374, 509  
 Romagnolo, A., 246  
 Roman, H., 52  
 Romanoff, A. J., 551  
 Romanoff, A. L., 551  
 Roos, A., 192, 265, 278, 279  
 Root, W. S., 268, 273, 274, 328  
 Roper, J. A., 80, 83  
 Rose, B., 519  
 Rose, E., 153  
 Rose, J. E., 428, 430, 449, 480  
 Rose, W. C., 79  
 Rosenbaum, E. E., 255  
 Rosenbaum, H., 437, 457  
 Rosenbaum, J. D., 157  
 Rosenberg, B., 356  
 Rosenberg, H., 314, 403  
 Rosenberg, T., 146  
 Rosenblueth, A., 400, 404, 406, 421, 423  
 Rosenfeld, S., 387  
 Rosenfield, R. E., 253  
 Rosenhain, F. R., 123, 279  
 Rosenheim, M. L., 335  
 Rosenman, R., 355, 359  
 Rosenmund, H., 546  
 Rosenthal, M., 10  
 Rosenthal, O., 300  
 Rosenthal, R. L., 35, 255, 325  
 Rosin, A., 268  
 Roskam, J., 255  
 Ross, G., 162, 163, 375  
 Ross, G. T., 390  
 Ross, M. H., 7, 10, 38  
 Rossiter, R. J., 327  
 Rostorfer, H. H., 270  
 Roswit, B., 38  
 Roth, C. E., 352  
 Roth, F., 222  
 Roth, H. P., 181  
 Roth, J. L. A., 124  
 Roth, L. W., 277  
 Roth, M., 425  
 Rothballer, A. B., 334  
 Rothchild, I., 542  
 Rothenberg, M. A., 12, 399

Rothlin, E., 312, 331, 389, 459  
 Rothschild, Lord, 539  
 Rothschild, K., 189  
 Rothschild, K. E., 276  
 Rothstein, A., 11  
 Rothwell, J. T., 78, 82  
 Rottman, R., 61  
 Roughton, F. J. W., 273, 274  
 Roussel, F., 485  
 Routley, E. F., 221  
 Rovenstine, E. A., 453  
 Rowan, W., 540  
 Rowlands, E. N., 333, 385  
 Royer, 104  
 Rozendaal, H. M., 29  
 Rubin, A., 128  
 Rubin, A. J., 128, 272, 358  
 Ruch, T. C., 471, 473, 474, 475  
 Rudolph, G. G., 380  
 Ruhe, C. H. W., 326, 327  
 Rumsey, C. C., 275  
 Rupp, J., 528  
 Rushton, W. A. H., 403, 404, 499  
 Russ, E. M., 183  
 Russell, D. S., 39  
 Russell, F. C., 550  
 Russell, J. A., 86, 87, 508, 509  
 Russell, K. C., 222  
 Russell, W. R., 428, 475  
 Ruth, E. B., 101  
 Rutledge, E. K., 519  
 Ryan, F. J., 57, 60  
 Ryan, M. T., 193  
 Rybak, B., 15  
 Ryder, A., 255  
 Ryder, H. W., 190, 278  
 Rynearson, E. H., 157

## S

Sabin, H. S., 386  
 Sachs, E., Jr., 428, 447, 449  
 Sachs, J. J., 246  
 Sacks, J., 105  
 Sadhu, D. P., 293, 527  
 Sagerson, R. P., 277  
 St. George, R. C. C., 489  
 Sakami, W., 77  
 Sako, Y., 218  
 Salaverri, F., 498  
 Salazar, H. A., *see* Astesalazar, H.

Salisbury, G. W., 538, 539  
 Salisbury, P. F., 399  
 Salisbury, W. W., 29  
 Salomon, K., 76, 110  
 Salter, W. T., 526, 528  
 Saltzstein, H. C., 212, 216  
 Salvatore, C. A., 544  
 Samuels, L. T., 88, 157, 294, 304, 380  
 Sanchez, H., 218  
 Sanchez-Palomera, E., 218  
 Sanderson, M., 253  
 Sanderson, P. H., 378  
 Sándor, G., 191  
 Sandweiss, D. J., 212, 216  
 Sanford, K. K., 85  
 Sangster, W., 205  
 Santa, R. D., *see* Della Santa, R.  
 Santenoi, D., 183  
 Sapeika, N., 332  
 Saret, H. P., 304  
 Saris, D., 181  
 Sarkisov, S. A., 426  
 Sarnoff, S. J., 191, 277, 315, 346, 458  
 Sartorius, O. W., 158  
 Sauberlich, H. E., 81  
 Saunders, J. A., 182  
 Saunders, J. W., 452  
 Saunders, M. G., 383, 459  
 Sawyer, C. H., 449, 504, 543  
 Sawyer, W. W., 421  
 Saxton, J. A., 106  
 Sayers, G., 157, 505  
 Sayers, M. A., 88, 505  
 Scarborough, H., 229, 312  
 Schachner, H., 526  
 Schachter, B., 546  
 Schachter, M., 211, 450, 456  
 Schachter, R., 450  
 Schaefer, K. E., 179, 185, 186  
 Schafer, E. P. S., *see* Sharpey-Schafer, E. P.  
 Schaffenburg, C., 329  
 Schallek, W., 452  
 Scheer, B. T., 11, 294  
 Scheinberg, P., 246, 254  
 Schemm, F. R., 165  
 Schenker, V., 157  
 Scheurman, W. G., 320, 321, 459  
 Schiess, W. A., 371  
 Schiff, C. A., 228  
 Schiller, I. W., 192

Schiller, S., 513, 514, 515  
 Schilling, J. A., 166, 218  
 Schilling, K., 247  
 Schinz, H. R., 104  
 Schlapp, W., 311, 345  
 Schlenk, F., 225  
 Schlesinger, R. B., 211  
 Schlichter, J. G., 325  
 Schloerb, P. R., 166  
 Schloss, G., 389, 390  
 Schultz, F. W., 313, 355  
 Schmidt, C. F., 192, 271, 320, 321  
 Schmidt, G., 147  
 Schmidt-Nielsen, B., 154, 167  
 Schmidt-Nielsen, K., 167  
 Schmiterlöw, C. G., 192  
 Schmitt, F. O., 21, 437  
 Schnabel, T., 314, 350  
 Schneid, B., 10  
 Schneider, J. J., 548  
 Schneider, L. K., 60  
 Schneider, M., 192, 271, 321  
 Schneider, W. C., 17, 18, 19, 305, 306, 307  
 Schneiderman, H., 31, 167  
 Schneirla, T. C., 545  
 Schnell, F. P., 391  
 Schober, W., 455, 457  
 Schoedel, W., 318  
 Schoen, A. M., 222  
 Schoenfeld, R. C., 318  
 Schoepfle, G. M., 401, 405, 406, 408, 415, 436  
 Schofield, B., 212  
 Scholander, P. F., 279, 280  
 Schooner, M. L., 350  
 Schork, P. K., 33  
 Schorr, S., 386  
 Schrader, R., 15  
 Schreiber, H., 347  
 Schreiber, V., 540  
 Schreiner, E., 350  
 Schreiner, G. E., 334  
 Schreiner, L. H., 435  
 Schrek, R., 35  
 Schroeder, H. A., 165, 166, 312, 333, 382  
 Schubert, H., 370  
 Schubert, J., 76, 106  
 Schulman, M. P., 73, 86  
 Schultz, A. L., 251  
 Schultz, F. W., 152, 355  
 Schultz, H. H., 161  
 Schultze, A. B., 539  
 Schulz, J., 20

- Schulze, W., 320, 459  
 Schumacher, G. A., 451  
 Schwab, W., 191  
 Schwartz, B. M., 363  
 Schwartz, H. M., 108  
 Schwartz, I. L., 151, 164  
 Schwartz, R., 154  
 Schwartz, S., 37  
 Schwartz, T. B., 157  
 Schwartzkopf, W., 269  
 Schweitzer, A., 314  
 Schwerma, H., 191, 192, 274, 277  
 Scofield, E. H., 476  
 Scott, D., Jr., 455  
 Scott, J. C., 181, 182, 457  
 Scott, J. K., 385  
 Scott, W. G., 352  
 Scott, W. W., 384  
 Scoville, W. B., 427  
 Scow, R. O., 109  
 Seabury, J. H., 192  
 Sealock, R. R., 523  
 Sear, R. A., 78, 82  
 Seed, J., 332, 429, 447  
 Seegers, W. H., 238, 239, 240, 241, 243, 244, 248, 254, 255, 256  
 Seeler, A. O., 246  
 Seely, R. D., 192, 347, 349  
 SeEVERS, M. H., 224, 347  
 Segal, J., 497  
 Segal, M. S., 192  
 Segall, G., 470  
 Segaloff, A., 304, 333  
 Segers, M., 311  
 Seibel, R. E., 267, 277  
 Seifriz, W., 8  
 Seifter, J., 253, 505  
 Selander, P., 246  
 Seldin, D. W., 159, 160, 171  
 Selkurt, E. E., 164, 312, 322, 358  
 Selye, F. L., 387  
 Selye, H., 384, 387, 513, 517, 518  
 Sennett, L. W., 359  
 Setala, K., 38  
 Settlege, P. H., 425, 428  
 Severin, G., 190  
 Seymour, A. H., 32, 33  
 Seymour, F. F., 546  
 Seysenegg, A. T., *see* Tschermak-Seysenegg, A.  
 Shadle, O. W., 269  
 Shafei, A. Z., 192  
 Shaffer, H. E., 538  
 Shanberge, J. N., 239, 250, 251  
 Shanes, A. M., 192, 399  
 Shanklin, G. J., 428  
 Shapiro, H., 13, 149  
 Shapiro, H. H., 192  
 Shapiro, S., 148, 244, 251, 255  
 Sharafyan, M. A., 278  
 Sharp, E. A., 256  
 Sharpey-Schafer, E. P., 320, 350  
 Shaub, H. G., 130  
 Shaw, B. M., 324  
 Shaw, B. W., 193  
 Shaw, J. H., 506, 509  
 Shaw, R. S., 317, 351  
 Shaw, W. M., 453  
 Shay, H., 215, 218, 223, 460  
 Shay, J. R., 53  
 Shea, A., 154  
 Shea, E., 192, 269  
 Shea, P. J., 193  
 Sheets, R. F., 327  
 Sheft, B. B., 276  
 Sheldon, M., 209  
 Shelford, W. O., 190  
 Shemin, D., 76, 77, 268  
 Shenkin, H. A., 271, 320, 321, 334, 429, 459, 475  
 Sherman, H. C., 550  
 Sherman, I. C., 436  
 Shettles, L. B., 545  
 Shimbel, A., 422  
 Shinowara, G. Y., 253  
 Shipley, R. E., 387  
 Shive, W., 79, 82  
 Shkurman, P. O., 278  
 Shlaer, S., 497, 498  
 Shock, N. W., 193, 327  
 Sholes, D. M., 314, 448  
 Shorr, E., 127, 164, 296, 299, 329, 382, 387  
 Shorvon, L. M., 34  
 Shteinberg, D. E., 278  
 Shull, W. H., 245  
 Sicher, H., 101  
 Sidwell, A. E., Jr., 192, 274  
 Siegel, B. M., 20  
 Siegel, P. S., 167  
 Siems, L. L., 316  
 Siffert, R., 39  
 Sigler, L. H., 314  
 Skahen, J. G., 158, 333  
 Skanse, B. N., 29  
 Skogland, C. R., 417  
 Silber, R. H., 529  
 Silberberg, M., 107, 111  
 Silberberg, N., 106  
 Silberberg, R., 107, 110, 111  
 Silbermann, L., 106  
 Silver, A. F., 323  
 Silver, H., 383  
 Silver, M. L., 192  
 Silver, P. H., 104  
 Silverman, L., 193  
 Silverstone, H., 92  
 Simkin, B., 383, 523  
 Simmonds, S., 75, 81  
 Simmonds, W. J., 279  
 Simon, A., 271  
 Simon, M. A., 216, 229  
 Simon, N., 39  
 Simon, S. E., 255  
 Simmons, E. L., 33  
 Simonsen, D. H., 326  
 Simpson, M. E., 86, 87, 92, 101, 108, 109, 508, 509, 528, 549  
 Simpson, R. G., 227  
 Sims, E. A. H., 88  
 Sinclair, D. C., 437  
 Sinclair, J. D., 452  
 Sinclair-Smith, B. C., 163, 164  
 Sinden, J. A., 551  
 Singer, K., 246, 251  
 Singer, M., 112  
 Singer, T. P., 30  
 Sipe, C. R., 33, 34  
 Siple, H., 218  
 Sirius, T., 451  
 Sirnes, 435  
 Sirola, J. H., 381  
 Siskel, J., 417  
 Sisson, J. H., 163, 164  
 Sjöstrand, F., 500  
 Sjöstrand, T., 192, 274, 321, 325  
 Slater, C. R., 548  
 Sleator, W., Jr., 192, 279  
 Slessor, A., 516  
 Slessor, C., 104  
 Sloan, R. D., 384  
 Slocumb, C. H., 516, 517  
 Slonimski, P. P., 62  
 Smedal, H. A., 190  
 Smiles, J., 7  
 Smirk, F. H., 332, 357  
 Smit, A. J. H., *see* Haagen-Smit, A. J.  
 Smith, A. G., 20  
 Smith, B. C. S., *see* Sinclair-Smith, B. C.  
 Smith, C. A., 160, 167

- Smith, D. E., 130, 139  
 Smith, E. D., 122  
 Smith, E. L., 86, 157, 497, 508  
 Smith, E. R., 385  
 Smith, F. R., 192  
 Smith, G. C., 111  
 Smith, G. P., *see* Parsons-Smith, G.  
 Smith, H. L., 516, 517  
 Smith, H. W., 159, 161, 162, 163, 370, 372  
 Smith, J. R., 161, 193  
 Smith, L. A., 476  
 Smith, L. H., 192  
 Smith, P. K., 188  
 Smith, R. E., 278  
 Smith, R. H. N., *see* Nimmo-Smith, R. H.  
 Smith, S. E., 101  
 Smith, T. R., 253  
 Smith, W. K., 429, 446, 447  
 Smith, W. W., 33, 40, 192  
 Smithwick, R. H., 312, 334, 352, 453  
 Smyth, H. G., 356  
 Smyth, N. P. D., 192  
 Snape, W. J., 219, 221, 229  
 Snapp, F. E., 277  
 Snapper, I., 10  
 Snellman, O., 252  
 Snider, C., 29, 436  
 Snyder, L. H., 47  
 Sobel, A. E., 106  
 Soberman, R. J., 150, 151  
 Soberon, J., 363  
 Sodi-Pallares, D., 363  
 Soffer, L. J., 505  
 Sokoloff, L., 157  
 Solhjell, I., 82  
 Soloff, L. A., 165, 334  
 Solomon, A. K., 73, 74, 80  
 Solomon, H. C., 450  
 Solomon, R. L., 499  
 Somkin, E., 275  
 Sommer, A. J., 221  
 Sommermeyer, K., 32  
 Sondergaard, E., 245  
 Sonne, L. M., 182, 385  
 Sonneborn, T. M., 47, 63, 65, 66  
 Sorensen, C. W., 192  
 Sorenson, C., 359  
 Sosman, M. C., 272  
 Sostman, E. R., 293  
 Soto-Rivera, A., 320  
 Soucek, B., 280  
 Soullairac, A., 471  
 Soulier, J. P., 246, 248, 249, 250  
 Soule, D. F., 294  
 Soule, S. D., 544  
 Soumireu, J., 547  
 Sparrow, A. H., 14  
 Spealman, C. R., 124, 167, 268, 327, 328, 329  
 Spear, F. G., 32  
 Specht, H., 154, 189, 193, 275  
 Speck, J. F., 75  
 Speert, H., 550  
 Spencer, F., 272, 359  
 Spencer, J. N., 191, 192, 277  
 Spencer, M. P., 164, 322  
 Sperry, R. W., 425, 481  
 Spicer, D. S., 253  
 Spicer, S. S., 192  
 Spiegel, E. A., 432, 433, 435, 449  
 Spiegel-Adolph, M., 105  
 Spinks, J. W. T., 105  
 Spiro, R. K., 191  
 Spitz, E. B., 320, 321, 459  
 Spivey, M., 550  
 Spoor, H. J., 120, 192  
 Sprague, J. M., 435  
 Spring, H., 153  
 Spritzler, R. G., 348  
 Spurrell, W. R., 212  
 Squires, R. D., 163, 164  
 Srb, A. M., 57  
 Srere, P. A., 511  
 Stacy, R. W., 120, 191, 192, 266  
 Stadie, W. C., 302, 521  
 Stadler, L. J., 52  
 Stämpfli, R., 401  
 Stanley, M. M., 524  
 Stanley W. C., 428  
 Stannard, J. N., 183, 192, 273  
 Stanton, J. R., 325, 352  
 Stanton, W., 357  
 Stapleton, G. E., 39  
 Stare, F. J., 299, 300  
 Stark, F. M., 39  
 Starr, H., 447  
 Starr, I., 161, 189, 275  
 Stauffer, H. M., 29  
 Stauffer, J. F., 301  
 Stavvaky, G. W., 209, 460  
 Stead, E. A., 277  
 Stead, E. A., Jr. 161  
 Stead, J. K., 380  
 Stead, W. W., 334  
 Stearner, S. P., 34  
 Steele, J. M., 150, 356  
 Stefanini, M., 239, 241, 242, 243, 244, 245, 246, 247, 248, 250, 251, 255  
 Steffee, C. H., 295  
 Stefko, P. L., 214  
 Steggerda, F. R., 38, 190, 222, 228, 332, 460  
 Steiger, W. A., 272, 358  
 Steigmann, F., 211, 213, 216, 226, 453  
 Stein, H. J., 126  
 Stein, I., 358  
 Stein, I. F., 205  
 Stein, I. F., Jr., 215, 216  
 Stein, S. N., 192, 424, 431  
 Stein, W. H., 72  
 Steinberg, I., 352  
 Steinhilber, A. H., 290  
 Steins, A. M., 391  
 Stephen, C. R., 181  
 Stephenson H. V., 109  
 Stephenson, M. L., 75, 85, 90  
 Stepka, W., 73, 77  
 Stepto, R., 295  
 Stern, K. G., 19, 20  
 Stetten, De W., Jr., 208  
 Stettner, C. E., 509  
 Stevens, C. D., 277, 278  
 Stevenson, I. P., 456  
 Stevenson, J. A. F., 447, 448, 449  
 Steward, F. C., 73  
 Stewart, H. J., 192, 359  
 Stewart, H. L., 227  
 Stewart, M., 252, 253  
 Stewart, T., 330, 352  
 Stickney, J. C., 192, 223, 313  
 Stiles, W. S., 497, 498  
 Stock, F. E., 383  
 Stoerk, H. C., 529  
 Stohl, A., 403  
 Stokes, J., 3rd, 192  
 Stokes, J. J., 157  
 Stokinger, H. E., 192  
 Stokstad, E. L. R., 79  
 Stoll, A., 389  
 Stoll, A. M., 121  
 Stone, C. A., 193  
 Stone, D., 148  
 Stone, F., 206, 476  
 Stone, R. S., 33  
 Stone, W. E., 192, 271  
 Stone, W. S., 58, 60, 61  
 Stoner, H. B., 353  
 Storaasli, J. P., 33, 249, 326

Stormont, C., 67  
 Stotz, W., 351  
 Stowe, L., 165  
 Strajman, E., 273  
 Strangeways, D. H., 267  
 Straub, E., 294  
 Straube, R. L., 37  
 Strauss, E., 519  
 Strauss, M. B., 157  
 Strausser, H., 399  
 Streicher, E., 123  
 Streicher, J. A., 78, 80, 82  
 Streiff, E. B., 458  
 Stricker, F. L., 108  
 Striebach, M. J., 19  
 Stroink, J. A., 543  
 Ström, G., 209, 448, 449  
 Strom-Olsen, R., 428  
 Stroud, M., 358, 458  
 Ströun, G., 276  
 Strumza, M. V., 191, 192, 277  
 Stubbs, A. L., 487  
 Stuckey, H. L., 167  
 Studer, A., 248  
 Studitskii, A. N., 109  
 Stuhlmann, M., 269  
 Stullken, D. E., 123  
 Sturkie, P. D., 36, 363  
 Sturm, H., 324  
 Stutinsky, F. S., 449  
 Styles, B., 252  
 Suarez, J. R. E., 182, 192  
 Suckie, H. M., 425  
 Sue, P., 110  
 Sugar, O., 424  
 Sugioka, K., 192, 279  
 Suhrie, V., 377  
 Sullivan, W. J., 540  
 Sulon, E., 107  
 Summers, J. E., 333, 384  
 Summerson, W. H., 302, 303, 307  
 Sunderman, F. W., 108, 153  
 Surtshin, A., 192, 193, 329  
 Susca, L. A., 192  
 Suskind, M., 183  
 Sussman, A. H., 193  
 Sussman, M. L., 363  
 Sutherland, G. B. B. M., 73  
 Sutherland, J. E., 79  
 Sutherland, V., 271  
 Sutton, G. C., 352  
 Swalue, L., 255  
 Swank, R. L., 278, 432  
 Swan, H., 185  
 Swann, H., 348

Swann, H. G., 191, 481  
 Swann, M. M., 16  
 Swanson, C. P., 48  
 Swanson, E. W., 538  
 Swanson, P., 550  
 Swayne, V., 246  
 Sweat, M. L., 88, 304  
 Sweeney, J. S., 386  
 Sweet, W. H., 429, 447  
 Swenson, P. C., 229  
 Swift, M. N., 37, 122  
 Swift, R. W., 294, 295  
 Swinyard, E. A., 122  
 Swyer, G. I. M., 539  
 Sykes, E. M., 240  
 Sykes, J. F., 540  
 Sylvester, G. E., 192  
 Sylvester, O., 517  
 Sylvén, B., 252  
 Synge, R. L. M., 72  
 Szego, C. M., 87, 507, 509, 515  
 Szentagothai, J., 435, 461  
 Szent-Györgyi, A., 21  
 Szilagyi, N., 192  
 Szymanski, T. A., 295

## T

Taffel, M., 168  
 Tagliamonte, B., 181  
 Tagnon, H. J., 249  
 Tahmistan, T. N., 193  
 Takáts, G. de, *see* De Takáts, G.  
 Talairach, J., 432  
 Talawach, J., 430  
 Talesnik, J., 295, 455, 456  
 Talso, P. J., 376  
 Tanabe, T. Y., 541  
 Tannenbaum, A., 92  
 Tanner, J. M., 349  
 Tansley, K., 32, 490, 491, 494  
 Tanturi, C. A., 252  
 Taquini, A. C., 182, 192  
 Tarail, R., 148, 159, 160, 171  
 Taran, L. M., 192  
 Tardieu, C., 461  
 Tardieu, G., 461  
 Tarver, H., 73  
 Tasaki, I., 399  
 Tatum, E. L., 49, 53, 75  
 Taurog, A., 88, 526, 528  
 Tavlitzi, J., 62  
 Tayes, M. A. F., 541  
 Taylor, B., 31  
 Taylor, B. E., 192, 267, 278, 324, 348, 351  
 Taylor, C. B., 138, 188, 189, 190, 274, 275  
 Taylor, C. L., 125  
 Taylor, C. M., 293  
 Taylor, E., 246  
 Taylor, E. S., 78, 80  
 Taylor, H. J., 190, 276  
 Taylor, H. L., 153, 456  
 Taylor, J. G., 158  
 Taylor, L., 130  
 Taylor, L. T., 28, 29  
 Taylor, R. D., 334, 383, 388, 458  
 Tcheng, K. T., 454  
 Tcherkoff, V., 272  
 Teas, H. J., 54, 57  
 Tehou-Su, 545  
 Ten Cate, J., 432  
 ten Doesschate, J., 499  
 Teorell, T., 399  
 Tepperman, H. M., 192, 276, 508  
 Tepperman, J., 192, 276, 504, 508, 513  
 Teräskeli, H., 498  
 Terrier, J. C., 332  
 Terry, M. C., 470  
 Tessmer, C., 34  
 Tetel'baum, A. G., 278  
 Teuber, H. L., 449  
 Teucq, E., 102  
 Thannhauser, S. J., 147  
 Thauer, R., 132  
 Thérain, M., 123, 512  
 Therman, P. O., 490, 509  
 Theron, P. A., 456  
 Thibault, C., 538, 542  
 Thibault, O., 527  
 Thiéblot, L., 183  
 Thimann, K. V., 546, 549  
 Thomas, C. B., 266  
 Thomas, J. E., 216, 220, 221, 227, 460  
 Thomas, N., 391  
 Thometz, A. F., 191, 277  
 Thompson, C. E., 451  
 Thompson, E. C., 33, 192  
 Thompson, E. M., 127, 291  
 Thompson, H. P., 19, 20, 23  
 Thompson, J. S., 191  
 Thompson, S. A., 191  
 Thompson, W. N., 318  
 Thomsen, P., 363  
 Thomson, A. E., 313  
 Thomson, J. A., 112

Thomson, J. D., 540  
 Thomson, L. C., 492, 496, 499  
 Thorn, G. W., 157, 192, 510, 516  
 Thorp, W. T. S., 538  
 Thorsen, G., 246  
 Threefoot, S., 161  
 Thunberg, T., 105  
 Thyburg, W. G., 549  
 Tichy, V. L., 324  
 Tieche, H. L., 224  
 Tiffeneau, R., 192  
 Timm, C., 312  
 Tinsley, C. M., 157  
 Tishkoff, G. H., 73, 166  
 Tjio, J. H., *see* Hin Tjio, J.  
 Tkacz, L. P., 221, 460  
 Tobian, L., 167, 519  
 Tobias, C. A., 30, 105, 273  
 Tobias, C. W., 255, 325  
 Toby, C. G., 514  
 Tocantins, L. M., 249, 252  
 Todd, R. L., 313, 332  
 Toffoli, C., 279  
 Tolbert, B. M., 74  
 Tolpin, M., 121  
 Toman, J. E. P., 122, 399, 432  
 Tomlin, S. G., 21  
 Tompkins, H. E., 311, 346  
 Tonbin, E. J., 460  
 Toomey, J. A., 107  
 Topper, Y. J., 299, 300  
 Torda, C., 269, 432  
 Tortella, E. P., *see* Pons-Tortella, E.  
 Tosteson, D. C., 449  
 Touroff, A. S. W., 356  
 Tow, P. M., 428  
 Towbin, E. J., 206, 253  
 Townsend, B. F., 449, 504, 543  
 Townsend, H. S., 313  
 Trabucchi, E., 217  
 Tracewell, T., 192  
 Trautman, W. V., 326, 327  
 Travis, B. L., 249  
 Trentin, J. J., 549  
 Trikojus, V. M., 506  
 Tripod, J., 349  
 Tripp, E., 334, 381  
 Tristram, G. R., 73  
 Trostorf, E., 192  
 Trott, J. C., Jr., 385  
 Trounce, J. R., 351  
 Trueta, J., 184, 373, 374,

378, 379, 382, 384, 390, 461  
 Truscott, B. L., 527  
 Tsai, C., 193, 237  
 Tschermak-Seysenegg, A., 485  
 Tucker, A. S., 362  
 Tuell, S. W., 237  
 Tuerkischer, E., 505  
 Tuft, H. S., 253  
 Tuft, L., 192  
 Tui, F. W. C., *see* Co Tui, F. W.  
 Tulin, M., 225  
 Tullar, B. F., 330, 455  
 Tullis, J. L., 34  
 Turman, W. G., 362  
 Turner, A. W., 506  
 Turner, C. W., 527, 528, 529  
 Turner, M. L., 140  
 Turrell, E. S., 193  
 Tuttle, W. W., 124, 131  
 Tweedy, W. R., 109  
 Twining, H., 542  
 Tyler, F. H., 157  
 Tyree, E. B., 37  
 Tytell, A. A., 73

## U

Udvardy, M. D. F., 252  
 Uehlinger, E., 108  
 Uerra, J. DeA., *see* De-Ajuriag-Uerra, J.  
 Uhley, M. H., 356  
 Ullmann, T. D., 386  
 Ullrich, F. W., 33  
 Ullrich, T. W., 34  
 Umbreit, W. W., 301  
 Uncapher, R. P., 34  
 Underwood, E. J., 547  
 Underwood, P. C., 540  
 Unger, P. N., 244  
 Ungewither, L., 370  
 Urist, M. R., 547  
 Urry, A. G., 266  
 Ussing, H. H., 12, 146, 147, 148, 399  
 Uvnäs, B., 209, 210, 212, 214, 227, 315, 330, 352, 358, 448, 449, 455  
 Uyeyama, K., 227

## V

Vail, E. G., 190  
 Valentine, W. N., 34, 35  
 Vallee, B. L., 269

Vanatta, J., 333  
 Vandam, L. D., 272, 277  
 Van den Ostende, M. J., 247  
 Vanderlaan, J. E., 525  
 Vanderlaan, W. P., 525  
 Vandermark, N. L., 539  
 van der Velden, H. A., 498, 499  
 Vander Werff, H., 82  
 Van der Werff, J. T., 32  
 van Dishoeck, H. A. E., 192  
 van Dongen, K., 331  
 Vane, J. R., 360  
 Van Eck-Vermande, G. J., 36  
 Van Goor, H., 179  
 Van Harreveld, A., 312, 431  
 Vanlerenberghe, J., 322  
 Van Liere, E. J., 192, 223, 224, 313, 329, 379  
 Van Loo, A., 192, 329  
 Van Metre, T. E., Jr., 107  
 Van Middlesworth, L., 192, 525  
 van Niel, C. B., 73  
 Van Slyke, D. D., 166, 266, 376, 379, 380, 384  
 Van Wagtendonk, W. J., 65  
 Varco, R. L., 278  
 Varley, H., 333, 385  
 Vartiainen, I., 268  
 Veall, N., 326  
 Vegh, L., 191  
 Velden, H. A., van der, *see* van der Velden, H. A.  
 Vendrely, C., 18  
 Vendrely, K., 18  
 Venning, E. H., 157  
 Verain, 104  
 Verhaart, W. J. C., 426, 435  
 Verloop, M. C., 184  
 Vermande, G. J. Van Eck, *see* Van Eck-Vermande, G. J.  
 Vermund, H., 433  
 Verney, E. B., 155, 381, 433  
 Verzar, F., 179, 191, 268, 275  
 Vial, J., 314  
 Victor, J., 334  
 Vigneaud, V. du, 83, 523  
 Villela, G. G., 18

Vincent, J., 102  
 Vislocky, K., 154, 171  
 Visscher, F. E., 212, 218, 377  
 Visscher, M. B., 138, 184, 185, 189, 192, 193, 389, 456  
 Vitcha, J. F., 357  
 Vivian, W. E., 424  
 Voegtli, W., 275  
 Vogel, W. C., 511  
 Vogt, M., 48, 508, 511, 512  
 Volk, B. W., 226  
 Volkmann, M., 277  
 Vollmer, E. P., 274  
 Vollmer, H., 107  
 Volwiler, W., 324  
 von Bonin, G., 428, 449, 474  
 Von Döbeln, W., 190  
 von Euler, C., *see* Euler, C. v.  
 von Euler, U. S., *see* Euler U. S. v.  
 Vonotzky, J., 124  
 Voorhees, A. B., 255  
 Vorchardt, P. R., 362  
 Vors, J., 544  
 Vouman, M. A., 498  
 Vries, A. de, *see* de Vries, A.  
 Vries, H. de, *see* de Vries, H.  
 Vrom, L., 251  
 Vroman, G. M. S., 251

## W

Waddell, D., 470  
 Waelsch, H., 83  
 Wagner, A., 357  
 Wagner, H., 253  
 Wagner, R. P., 50, 53  
 Wahlberg, T., 30  
 Waikoff, H. M., 251  
 Wakerlin, G. E., 334  
 Wakim, K. G., 331, 332  
 Walcott, W. W., 315, 328, 353  
 Wald, G., 487, 488  
 Waldman, J., 103  
 Waldo, C. M., 88, 112  
 Waldron, J. M., 221, 460  
 Walker, A. E., 154, 171, 432, 474  
 Walker, A. G., 311, 345  
 Walker, A. J., 316  
 Walker, A. M., 372, 380

Walker, E., 273  
 Walker, E. A., 453  
 Walker, J. M., 157  
 Walker, P., 192, 267  
 Walker, S. E., 246  
 Walker, S. M., 211, 215, 549  
 Walker, W. S., 193  
 Wall, G. D., 432  
 Wall, P., 447, 448, 449  
 Wallace, S. L., 158  
 Walls, D., 207  
 Walls, E. W., 352  
 Walter, C. J., 449  
 Walter, V. J., 423, 432  
 Walter, W. G., 423, 432  
 Walthard, B., 108  
 Walton, C. J., 161  
 Wang, C. C., 220, 221, 222  
 Wang, C. F., 153, 327  
 Wang, C. S., 450  
 Wang, H., 547  
 Wang, J.-C., 152  
 Wang, K. J., 216, 222  
 Wang, S. C., 228, 377, 435  
 Wangenstein, O. H., 216, 217, 218  
 Ward, A. A., Jr., 428, 430, 431, 434, 435, 446, 447  
 Ward, H. P., 164, 323  
 Ward, J. W., 426, 430  
 Ware, A. G., 238, 239, 240, 241, 243, 244, 245, 248, 254, 255  
 Warkany, J., 551  
 Warner, E. D., 246  
 Warren, J. V., 161, 277  
 Warren, S., 29, 36, 39  
 Warrick, F. B., 102  
 Warwick, R. T. T., 477  
 Washman, J., 523  
 Wasserman, L. R., 192, 278  
 Waterhouse, C., 384  
 Watkins, D. H., 224  
 Watson, C. J., 76, 156, 247, 251  
 Watson, C. W., 432  
 Watts, J. W., 428, 449  
 Waud, R. A., 193  
 Waugh, D. F., 21  
 Wayne, E. J., 353  
 Weale, R., 489  
 Weatherall, J., 184, 455, 457  
 Weatherford, H. I., 112  
 Weatherwax, J. L., 36  
 Weaver, F. L., 192  
 Webb, J. P., 277

Webb, R. L., 323  
 Weber, A. F., 544  
 Weber, G. M., 91  
 Weber, J. J., 428  
 Weber, R. P., 38, 332  
 Webster, D. R., 217  
 Webster, F., 423  
 Webster, J. E., 192, 271  
 Wedell, G., 424, 437  
 Weekers, R., 485  
 Weeks, J. R., 225  
 Wegria, R., 164, 323  
 Weiner, D., 272  
 Weiner, H. M., 350  
 Weiner, M., 251  
 Weinmann, J. P., 101  
 Weisberg, H. F., 522, 523  
 Weisiger, J. R., 266  
 Weiss, P., 14  
 Welander, A. D., 32, 33  
 Welch, F. V., 7  
 Wells, B. B., 79, 514  
 Wells, J. S., 137  
 Wells, L. J., 227  
 Welsh, J. H., 399, 452  
 Welt, L. G., 165  
 Wendel, G. E., 352  
 Wendel, L., 548  
 Wener, J., 210, 216, 229, 460  
 Went, F. W., 53  
 Wenzel, B. M., 476  
 Werff, H. V., *see* Vander Werff, H.  
 Werko, L., 189, 191, 277, 346, 349, 350  
 Werner, A. S., 72, 75  
 Werner, A. Y., 190  
 Wertheimer, E., 505  
 Wesson, L. G., 159, 372  
 Wesson, L. G., Jr., 159, 161, 162, 163  
 West, C. D., 159  
 West, G. B., 331  
 West, J. R., 370  
 West, R., 76  
 West, T. C., 225  
 Wester, M. R., 184  
 Wester, W. R., 356  
 Westergaard, M., 49  
 Western, F., 28  
 Westman, A., 37  
 Weston, R. E., 164, 278  
 Weterlings, P. A., 183  
 Wetzell, N. C., 252  
 Wezler, K., 189, 330  
 Weymouth, F. W., 485  
 Whaley, R. V., 274  
 Whatley, E. C., 158

- Wheatley, A. H. M., 299  
 Wheatley, M. D., 433  
 Wheeler, C. W., 520  
 Wheeler, E., 550  
 Wheeler, J. E., 222  
 Wheeler, N. C., 163, 277, 328, 379  
 Wheeler, P., 193, 206, 476  
 Whieldon, J. A., 431  
 Whipple, G. H., 166  
 Whitcher, C. E., 296  
 White, A., 87, 507, 509, 515  
 White, A. G., 165  
 White, C., 277  
 White, F. M., 123  
 White, H. L., 192, 278, 279, 295, 323, 374, 509  
 White, I. U., 296  
 White, J. C., 19  
 White, P. R., 84  
 White, W., 12, 13  
 White, W. A., 273  
 Whitehead, R. W., 191, 192, 277  
 Whitehorn, W. V., 190, 191  
 Whiteley, A. H., 11, 279  
 Whitten, W. K., 549  
 Whittenberger, J. L., 191, 277, 315, 346, 458  
 Whitteridge, D., 354, 452  
 Whitney, J. E., 508  
 Whitrock, R. M., 224  
 Whittier, J. R., 433  
 Whyte, M. M., 160  
 Wicks, W. R., 278  
 Widdas, W. F., 193  
 Wiener, M. J., 255  
 Wiener, N., 93, 400, 404, 406, 421, 422, 423  
 Wiersma, C. A. G., 452  
 Wiese, H. F., 154, 170  
 Wiesinger, K., 277  
 Wiggers, C. J., 349  
 Wiggers, H. C., 378  
 Wilburne, M., 325, 356  
 Wildman, S. G., 10  
 Wile, S. A., 251  
 Wiley, J. L., 327, 329  
 Wilhelm, A. E., 86, 508, 516  
 Wilk, A. L., 540  
 Wilkins, R. W., 157, 325, 334, 352, 359, 453  
 Wilkinson, E., 160  
 Williams, A. H., 312, 382  
 Williams, C., 361  
 Williams, C. R., 28, 29  
 Williams, E., 550  
 Williams, M. F., 543  
 Williams, R. H., 511  
 Williams, R. J., 220  
 Williams, R. W., 422  
 Williams, V. Z., 546  
 Williams, W. L., 17  
 Willmon, T. L., 180  
 Wills, C. G., 546  
 Wills, J. H., 373  
 Willstaedt, H., 102  
 Wilson, D. W., 106  
 Wilson, F. N., 361  
 Wilson, H. B., 192  
 Wilson, I. B., 192  
 Wilson J. G., 551  
 Wilson, M., 124  
 Wilson, M. L., 218  
 Wilson, P. F., 272, 359  
 Wilson, R. H., 184, 348  
 Wilson, S., 245  
 Wilson, W. L., 8, 15  
 Winge, O., 62  
 Winkelstein, A., 219  
 Winkler, A. W., 148, 152, 154, 166, 169, 170  
 Winnick, T., 73, 74, 75, 77, 79, 86, 90  
 Winslow, J. A., 163, 277, 379  
 Winsor, T., 351  
 Winter, O. S., 334, 388  
 Winzler, R. J., 83, 122, 525  
 Wirts, C. W., 219  
 Wirz, E., 279, 349  
 Wiseman, R. D., 108  
 Wislocki, G. B., 88, 103, 112  
 Wissler, R. W., 295  
 Witham, A. C., 109, 277, 451, 529  
 Witkin, E. M., 48  
 Wittenberg, J., 76  
 Wittenborg, M. H., 362  
 Wohlzogen, F. X., 87  
 Wolbach, S. B., 107, 246  
 Wolf, A. V., 149, 161, 169  
 Wolf, B. S., 28  
 Wolf, S., 228, 229, 334, 388, 456, 457  
 Wolfe, J. B., 428  
 Wolff, H., 334  
 Wolff, H. G., 229, 269, 388, 432, 451, 457  
 Wolff, J., 525  
 Wolfson, W. Q., 505  
 Wollack, A. C., 265  
 Wollaeger, E., 221  
 Wollenberger, A., 347, 360  
 Wolman, A., 28, 192, 274  
 Wolvekamp, H. P., 270  
 Womack, M., 79  
 Wong, Y. T., 153  
 Wood, E. H., 192, 267, 277, 278, 279, 312, 324, 348  
 Wood, F. C., 192  
 Wood, H. G., 299  
 Wood, J. E., 159, 541  
 Wood, J. E. Jr., 381  
 Wood, P., 351  
 Wood, T., 268  
 Woodbury, J. W., 399  
 Woodbury, L. A., 399, 432  
 Woodbury, R. A., 222  
 Woodford, R. B., 429, 459  
 Woods, J. W., Jr. 312, 352  
 Woods, L. A., 347  
 Woods, M., 19  
 Woods, M. W., 18  
 Woodward, E. R., 209  
 Woolley, D. W., 79, 82, 83, 84  
 Woolridge, R. L., 295  
 Woolsey, C. N., 425, 426, 428, 430, 449, 475, 480  
 Wootton I. D. P., 267, 268  
 Worstell, D. M., 292, 297  
 Wrenn, R. T., 540  
 Wretling, K. A. J., 332  
 Wright, H. P., 325  
 Wright, I. S., 249  
 Wright, N., 477  
 Wright, P. L., 541  
 Wright, W. D., 492  
 Wulff, M. H., 385  
 Wulff, V. J., 495  
 Wyburn, G. M., 104  
 Wycis, H. T., 432, 433, 449  
 Wyckoff, H., 28, 29  
 Wyckoff, H. O., 29  
 Wyckoff, R. W. G., 20  
 Wyman, J., 267  
 Wyngaarden, J. B., 347  
 Wyss, O., 58, 60, 61  
 Wyssling, A. F., *see* Frey-Wyssling, A.

- Yaglou, C. P., 129  
 Yakovlev, P., 429  
 Yakovlev, P. I., 445, 447  
 Yamamoto, W., 124, 167  
 Yanow, M., 544

Yaskin, J. C., 459  
 Yeagley, J., 213  
 Yeakel, E. H., 334  
 Yiengst, M. J., 193  
 Voffey, J. M., 192, 510  
 Yonkman, F. F., 224  
 York, G. E., 271  
 Youmans, W. B., 193, 357  
 Young, C. W., 477  
 Young, F. G., 521  
 Young, I. I., 246  
 Young, N. F., 514  
 Young, W., 160, 167  
 Young, W. C., 111  
 Younger, F., 107  
 Yudkin, S., 160, 167

Yudowitch, K., 21

## Z

Zable, M., 428  
 Zalokar, M., 56  
 Zamecnik, P. C., 75, 85, 90, 91  
 Zapp, J. A., Jr., 302  
 Zarrow, M. X., 548  
 Zatti, P., 239  
 Zatuchni, J., 165  
 Zechmeister, L., 53  
 Zegers, R. T., 499  
 Zeligs, M. A., 457  
 Zeltmacher, K., 251

Zerahn, K., 106, 325  
 Ziegler, R. F., 192, 278  
 Zierler, K. L., 193, 253  
 Zinsser, H., 312, 352  
 Zirkle, R. E., 31  
 Zlotnik, I., 545  
 Zollinger, H. V., 17  
 Zotterman, Y., 314, 354, 454, 473  
 Zucker, M. B., 237  
 Zweifach, B. W., 164, 387  
 Zweig, M., 211, 213, 453  
 Zwilling, E., 521  
 Zwirn, P., 323, 458  
 Zylstra, W. G., 279

## Subject Index

### A

- Acetylbetamethylcholine, gastric secretion and, 210
- Acetylcholine
  - gastric secretion and, 209-10
  - heart and, 360
  - synaptic activity and, 452
- Acid-base balance, respiration and, 182-83
- Acidosis
  - asphyxia and, 276-77
  - sodium in cells and, 170
  - water distribution and, 171
- Acriflavin, mutagenic properties of, 48
- Addison's disease, *see* Adrenal gland
- Adenosinetriphosphate
  - adrenal cortical secretion and, 512
  - heart rate and, 353-54
  - peptide synthesis and, 75
  - tissue metabolism and, 303-4
- Adipose tissue, glycogen in, 522-23
- Adrenal cortex, 509-19
  - adrenal cortical extract, glycogenesis and, in gastric cancer, 514
  - altitude tolerance and, 188
  - arginase activity and, 516
  - bone growth and, 108
  - carbohydrate metabolism and, 514, 516
  - cardiac edema and, 164
  - cartilage formation and, 108
  - cholesterol in, 511
  - Cushing's syndrome, 155
  - gouty arthritis and, 518
  - hormones of
    - arthritis, rheumatoid, and, 516-17
    - Compound E, 514, 516-18
    - rheumatic fever and, 517
    - stress responses and, 518-19
  - see also* individual substances: Des-oxycorticosterone, etc.
  - hypertension and, 387-88
  - ketone in blood and, 515-16
  - kidney function and, 157-58, 384
  - metabolism of, 511-13
    - adenosinetriphosphate and, 512
    - adrenocorticotrophic hormone and, 511-13
    - ascorbic acid and, 512-13
    - pantothenic acid and, 513
    - protein metabolism and, 513-15
    - radiation and, 37
    - steroid hormone production in, 509-11
    - adrenocorticotrophic hormone and, 510, 511-12
- Adrenal cortex (*cont.*)
  - steroid hormone production in (*cont.*)
    - gonadotropins and, 510-11
    - sweat composition and, 155
  - x-zone, 510, 549
- Adrenal gland
  - hypertrophy of, in cold, ascorbic acid and, 123
  - neuroeffector substance, 454
  - norepinephrine secretion of, 330
- Adrenocorticotrophic hormone, *see* Pituitary, anterior
- Age, arterial pressure and, 313
- Alarm reaction, 505
  - carbon dioxide concentration and, 186
- Alcohol
  - kidney and, 385
  - pituitary inhibition by, 157
- Alkalosis, fever and, 269
- Alleles, 51-52, 55
- Allergic conditions, thrombocytopenia and, 251
- Altitude
  - adaptation to, 186-88, 275
  - anoxia and, 274-76
  - body temperature and, 189
  - cardiac output and, 189
  - circulation and, 275
  - lactic acid accumulation and, 276
  - oxygen consumption and, 189
  - pressure breathing and, 189-90
  - red cell count and, 187-88
  - reproduction and, 541
  - tolerance to, 186-88
    - adrenal cortex and, 188
    - cytochrome-c and, 188
    - diet and, 188
    - methylene blue and, 188
    - nicotinamide and, 188
    - nicotinic acid and, 188
    - oxygen breathing and, 275-76
    - red cell count and, 187-88
- Amino acids
  - antibiotic activity, 82-83
  - balance of, 82
  - in blood
    - growth hormone and, 523
    - insulin and, 523
  - bone and, 104
  - cell growth and, 84-85
  - distribution of, 78-79
    - in fetus, 78
  - interconversions of, 77-78
  - metabolism of, measurement of, 73
  - requirements, 79-82

- Amino acids (*cont.*)  
 synthesis of, 77-78  
 transport of, across cell membranes, 78-79  
 urea cycle and, 77  
*see also* specific amino acids
- Aminophyllin  
 coronary vasodilation and, 272  
 heart and, 358
- Anaphylactic shock, adrenocorticotrophic hormone and, 519
- Androgens, 548-49  
 bone and, 111  
 castration and, 548  
 excretion of, 548  
 lactation and, 548  
 ovariectomy and, 548
- Anemia, pernicious, red cell production and, 76
- Anemia, sickle cell  
 red cell production and, 76  
 renal cortical necrosis and, 384
- Anesthesia  
 blood volume and, 327  
 pentothal, respiration and, 183  
 spinal  
   blood flow and, 334  
   blood pressure and, 390
- Anoxemia, *see* Oxygen deficiency
- Anoxia, *see* Oxygen deficiency
- Antibodies, proteins in diet and, 80-81
- Antifibrinolysin, 255
- Antigens  
 in *Paramecium*, 65-67  
 production of, gene control of, 66-67
- Antihistamine drugs  
 cathartic drug action and, 225  
 gastric secretion and, 213-14  
 hyperemia and, 318  
 intestinal spasm and, 224-25  
 vasomotor phenomena and, 316  
*see also* specific substances
- Antipyrine, extracellular fluid measurement and, 150-51
- Antlers  
 castration and, 88-89  
 hormones and, 88-89, 111-12
- Appetite, olfactory thresholds and, 476-77
- Arginase  
 adrenal cortex and, 516  
 hormones and, 509
- Arterial pressure, 313  
 age and, 313  
 blood glucose and, 121  
 body temperature and, 121  
 body weight and, 313  
 cerebral circulation and, 321-22  
 cerebral cortex and, 428-29
- Arterial pressure (*cont.*)  
 desoxycorticosterone acetate and, 333  
 emotional stress and, 456  
 gravity and, 316-17  
 heat stress and, 125  
 kidney and, 333-34  
 measurement of, 311-12  
 pregnancy toxemia and, 388  
 spinal anesthesia and, 390  
 temperature regulation and, 134  
 tetraethylammonium and, 334-35, 388  
 vasomotor phenomena and, 314-16
- Arteriovenous aneurysm, cardiac output and, 350-51
- Arthritis, rheumatoid, adrenal cortical hormones (compound E) and, 516-17
- Ascites  
 diet and, 166  
 edema and, 166
- Ascorbic acid  
 adrenal cortex and, 512-13  
 adrenal hypertrophy in cold and, 123  
 steroid interconversion and, 513  
 in tissues  
   adrenal hypertrophy in cold and, 123  
   hypothermia and, 123  
*see also* Vitamin C
- Asphyxia  
 acid-base changes in, 276-77  
 anoxia and, 329-30
- Atmospheric pressure, decompression, 190
- Atropine  
 gastrointestinal motility and, 222-23, 224  
 heart rate in hypothermia and, 123  
 pituitary hormone secretion and, 504
- Autonomic nervous system, 445-62  
 nerve fiber types in, 455  
 shock therapy and, 450
- Aviation physiology  
 respiration, 186-90  
*see also* Altitude; Oxygen deficiency; Respiration, pressure breathing; etc.

## B

- Bacitracin, peptide nature of, 83
- Bacteria  
 amino acids as inhibitors of, 82-83  
 genetics of, 57-61  
 mutations in, 49  
   ultraviolet radiation and, 60-61  
 penicillin resistance of, 78  
 sexual reproduction in, 57-58  
 streptomycin resistance of, 59-60  
 submicroscopic structure of, 20
- Bacteriophage  
 mutations of, 57, 61-62

- Bacteriophage (*cont.*)  
  mutations of (*cont.*)  
    ultraviolet radiation and, 62  
  production of, 20  
  radiation and, 31  
  resistance to, 57-60
- Barbiturates, respiration and, 181
- Basal metabolism, 290-92  
  climate and, 291-92  
  malnutrition and, 292  
  standards of, 290-91  
  surface area and, 296-98  
  thyroid gland and, 295  
  ventilation rate and, 292
- Benadryl, gastric secretion and, 211
- Bends, 190
- Bile, secretion of, 218, 219-20
- Bilirubin, excretion of, 220
- Biosynthesis, genes and, 53-57
- Bladder, urinary, cerebral cortex and, 430
- Blood  
  alveolar-arterial equilibrium, 265-67  
  carbonic anhydrase in, 269  
  clotting of, *see* Blood clotting  
  flow of, *see* Blood flow  
  gas transport, 265-80  
    anesthetics and, 278  
    in brain, 270-71  
    in heart muscle, 272  
    in kidney, 273  
    in liver, 272  
    of nitrogen, 278  
  hematocrit values of, blood volume and, 325-26  
  oxygen saturation of  
    alveolar air and, 266  
    oxygen concentration in air and, 266-67  
  pressure, *see* Arterial pressure and Venous pressure  
  respiratory functions of, 265-80  
  sugar, *see* Glucose, of blood  
  temperature of, 128-30  
  viscosity of, red cell count and, 313  
  volume of, *see* Blood volume  
  x-ray radiation and, 32-34
- Blood clotting, 237-56  
  Ac-globulin and, 239-43  
  albumin and, 253  
  calcium and, 248  
  clot retraction, 250  
  hemophilia and, 238-39, 242-43  
  heparin and, 252-53  
  inhibitors of, 252-53  
  labile factor, 240-42  
  liver disease and, 252  
  measurement of, 255  
  platelets and, *see* Platelets, blood  
  prothrombin and, *see* Prothrombin
- Blood clotting (*cont.*)  
  radiation and, 33-34  
  theories of, 238-39  
  thrombin and, 248  
  thrombinogenic cycle, 238-39  
  thrombocytopenia and, 242-43  
  thromboplastic agents and, 248-49  
  thromboplastic enzymes and, 248-49
- Blood flow  
  drugs and, 330-32  
  hemodynamics and, 312-13  
  hyperemia, antihistamine drugs and, 318  
  measurement of, 270-71, 311-12  
  in organs, *see* specific organs  
  peripheral resistance and, 312-13  
  skin temperature and, 319  
    as index, 130
- Blood volume, 325-28  
  anesthesia and, 327  
  edema and, 164-65  
  epinephrine and, 327  
  exercise and, 327  
  heat and, 327-28  
  measurement of, 325-27  
  pressure breathing and, 328
- Bone  
  androgens and, 111  
  birefringence of, 101  
  calcification, abnormal, vitamin D excess and, 108  
  calcium compounds in, 102-5, 107  
  carbonato-apatite in, 104  
  chemical nature of, 104-5  
  circulation in, 101  
  development of, 102-4  
    adrenocorticotrophic hormone and, 108  
  chemical aspects of, 102-4, 107  
  enzymes and, 102-5, 107  
  growth hormone and, 108, 528  
  osteogenin and, 102  
  parathyroid gland and, 109  
  pH and, 102  
  phosphatase and, 102-4  
  radiation and, 39, 102  
  thyroid gland and, 109  
  thyroxine and, 528  
  dietary factors and, 106-8  
  diffraction spectrum of, 104  
  fluorine and, 106  
  glycogen in, 107  
  hormones and, 108-112  
  hyperostosis, vitamin C deficiency and, 107  
  marrow, *see* Bone marrow  
  metabolism of, 105  
    parathyroid and, 528-29  
  minute structure of, 101

**Bone** (*cont.*)

- organic constituents of, 105
- ossification of, *see* Bone, development of
- osteopetrosis, rickets and, 107
- phosphatase in, 102-4
  - amino acids and, 104
- phosphorus compounds in, 102-5, 107
- refractive index of, 101, 104
- repair of
  - phosphatase and, 104
  - vitamin C deficiency and, 104, 107
- structure of, 101-2

**Bone marrow**

- oxygen saturation of, 268
- radiation and, 33-34

**Brain**

- circulation in, 270-71, 320-22, 459
    - arterial pressure and, 321-22
    - diabetes and, 321
    - intracranial pressure and, 321
    - regulation of, 271
    - tumors, cerebral, and, 321
  - diencephalon, 432-33, 448-450
  - electrical activity of, 432
  - electroencephalography, 432
  - error source in, 495
  - glycolysis in, enzymes and, 304
  - metabolism
    - enzymes and, 303-4
    - succinate and, 299-300
  - radiation and, 39
  - respiration of, pH and, 302-3
  - reticular formation of, 433-35
  - rhythmic activity and, 434-35
  - stem, 433-35
    - Parkinson's disease, 434
    - vasospasm in, 459
    - see also* Cerebral cortex
- Burns, edema in, 152

**C**

- Caffeine, mutagenic properties of, 48
- Calcification, of bone, *see* Bone
- Calcium
  - blood clotting and, 248
  - fibrinogen and, 254
- Cancer
  - diagnostic screen test for, 92
  - genetics of, 47
  - see also* Carcinogenesis and Growth, neoplastic
- Capillaries
  - circulation in, 323-24
  - permeability of, 323-24
- Carbohydrate
  - in diet, specific dynamic action of, 294
  - metabolism of, adrenal hormones and, 514, 516, 518

**Carbohydrate** (*cont.*)

- phosphorylation of, potassium transport and, 147-48
- Carbon dioxide
  - concentration in air
    - alarm reaction and, 186
  - respiration and, 185-86
  - effects of, 192
  - respiration and, 182-83, 185
- Carbon monoxide
  - elimination of, 273
  - poisoning, resuscitation from, 274
  - tolerance to, 273-74
- Carbonato-apatite, in bone, 104
- Carbonic anhydrase
  - in blood, 269
  - gastric secretion and, 207
- Carcinogenesis
  - diet and, 92
  - growth hormone and, 92-93
  - protein metabolism and, 91
- Carcinogens, enzymes and, 91-92
- Cardiac output
  - altitude and, 189
  - anoxemia and, 351
  - arteriovenous aneurysm and, 350-51
  - measurement of, 277-78, 348-49
  - oxygen intake and, 350
  - pregnancy and, 350
  - respiration and, 349-50
  - right atrial pressure and, 346-47
  - temperature and, 355
- Carotid sinus
  - retinal blood vessels and, 458
  - vasodepression and, 314
- Cartilage
  - development of
    - adrenocorticotrophic hormone and, 108
    - pituitary growth hormone and, 108
  - riboflavin and, 107
- Castration
  - androgens and, 548
  - antlers and, 88-89
- Cathartics, antihistamine drugs and, 225
- Cells
  - cytolysis, 16-17
  - development of
    - amino acids and, 84-85
    - karyocytoplasm and, 14-15
    - nucleoprotein and, 14-15
  - ectoplasm, fibrils in, 19-20
  - endoplasm, granules in, 19
  - fibrillization, 21-23
    - adenosinetriphosphate and, 22
  - fractionation, 16-18
  - ionic exchange in, 145-50
  - membranes of, *see* Membranes, of cells
  - metabolism, *see* Metabolism, of tissues

Cells (*cont.*)

nucleus

- constituents of, 12
- cytoplasmic relation, 14-16
- x-ray radiation and, 10
- particulates of, 16-19
- structure of, 19-21
- submicroscopic structure of, 19-21
- see also* Cytoplasm and Protoplasm

Cerebellum

- sensory projections, 435-36
- vision and, 436

Cerebral cortex, 424-32

- arterial pressure and, 428-29
- bladder pressure and, 430
- circulation in, lobotomy and, 429
- depression, spreading, 430-31
- electrical activity of
  - electroencephalography, 432
  - error source in, 495
- electroencephalography, *see* Cerebral cortex, electrical activity of
- emotional centers of, 430, 446-47
- frontal lobes, 427-29
  - cerebral blood flow and, 429
  - oxygen consumption and, 429
  - specificity in, 427-29
  - stomach acidity and, 429
  - visceral functions and, 446-47
- functions of, 428-29
- gastrointestinal motility and, 448
- injury to, reorganization after, 425
- kidney size and, 448
- learning and, 425
- limbic lobe, 429-30
  - personality and, 430
- mesopallium, 446-48
- motor area, 425-27
  - localization in, 425-27
  - stimulation of, 425-26
- olfaction and, 479-81
- pyramidal tract, localization in, 426
- respiration and, 429, 447
- speech centers in, 424-25, 430
- stimulation of, 447-48
- suppression, 430-31
- suppressor area, spasm and, 435
- taste receptive area of, 474
- visual functions of, 425

Cerebrum, *see* Brain

Chemoreceptors, drugs and, 192-93

Chloralose, gastric secretion and, 209

Chloride

- excretion of
  - adrenal cortical hormones and, 154-55
  - heat and, 127

Cholesterol

- esterification of, adrenal cortex and, 511
- gonadotropins and storage of, 507-8

Cholinesterase, temperature regulation and, 135

Cinchophen, peptic ulcer and, 218

Circulation

- in organs, *see* specific organs
- peripheral, *see* Peripheral circulation
- salt depletion and, 169
- sodium depletion and, 169-70
- in special states, *see* Emotion, Muscular exercise, etc.

vasomotor control of, 314-16

Circulation time, 324-25

Citric acid, sperm metabolism of, 540

Cochlea, frequency analysis in, 423

Cold, *see* Temperature

Cold pain, 124, 131, 133

Colon

- colitis, psychological factors and, 229
- flatus excreted from
  - composition of, 228-29
  - quantity, 228
- motility of,
  - inhibition of, 225
  - psychological factors and, 225

Color vision, *see* Vision

Comfort, temperature and, 129, 132-33

Compound E, Kendall's, *see* Adrenal cortex, hormones of

Convalescence, protein in diet and, 295

Corticosteroids, excretion of, edema of pregnancy and, 167

Corticosterone, kidney function and, 157-58

Creatinine, excretion of, heat and, 127

Cushing's syndrome, *see* Adrenal cortex, Cushing's syndrome

Cybernetics, 421-24, 445

Cytochrome-c, altitude tolerance and, 188

- constituents of, 10-12
- Hodgkin's disease and, 10
- media for study of, 17-18
- nucleus, relation to, 14-16

D

Decompression, *see* Atmospheric pressure, decompression

Defense mechanisms, protein in diet and, 80-81

Dehydration

- heat stress and, 126
- kidney function and, 168, 170
- salt and, 169
- water distribution and, 168

Demerol, diuresis and, 157

Desoxycholate, mutagenic properties of, 48

Desoxycorticosterone

adrenocorticotrophic hormone secretion and, 505-6

hypertension and, 332-33, 387-88

kidney function and, 157-58

radiation sickness and, 38

Deuterium oxide, extracellular fluid

measurement and, 150, 153-54

Devaux effect, in cytotoxicity, 17

Diabetes, experimental

adrenocorticotrophic hormone induced, glutathione effect on, 520

alloxan

fat feeding and, 520

pituitary hormones and, 521

Diabetes insipidus

adrenal cortical hormones and, 157-58

pitressin and, 158

Diabetes mellitus, 519-21

cerebral circulation in, 321

coma, vasomotor phenomena in, 320

emotional stress and, 456

potassium transfer and, 148, 171

sulphydryl compounds and, 519-20

"taste blindness" and, 470-71

Diarrhea, infantile, water distribution

and, 170-71

Dibenzamine, 328, 331, 334

heart and, 356-57, 358

ovulation and, 543

pituitary hormone secretion and, 504-5

Dicumarol

fetal death and, 246

prothrombin and, 244-46

vitamin K and, 245-46

Diencephalon, *see* Brain, Hypothalamus, and Thalamus

Diet

altitude and, 188

bone and, 106-8

carcinogenesis and, 92

Digestive system, 205-29

circulation in, 322

*see also* individual organs

Digitalis, 351

prothrombin and, 246

Dihydroergocryptine (DHE), 331

Dihydroergocorine (DHO), 331

Diodrast, kidney clearance of, 370-71, 372-73

Diphosphopyridine nucleotidase, tissue metabolism and, 303-4

Disease, defense mechanisms in, *see* Defense mechanisms

Diuresis, *see* Diabetes insipidus and Kidney, diuresis

Doryl, gastric motility and, 216

## E

Ear

cochlea, *see* Cochlea

frequency analysis in, 423

ringing in, 423

Edema, 161-67

in burns, 152

cardiac, 161-66

adrenal cortex and, 164

blood volume and, 164-65

diuresis and, 164

extracellular fluid and, 164-66

kidney function and, 161-66

plasma volume and, 164-65

sodium and, 161-66, 169-70

of pregnancy, 167

of premature infants, 167

protein deficiency and, 166

Eggs

development of, 14-16

fertilization of, 545

osmosis in, fertilization and, 11, 13

transfer of, 542

Electroencephalography, *see* Brain, electrical activity of; and Cerebral cortex, electrical activity of

Electrolytes

depletion of, 167-72

loss of, in sweat, 154-55

metabolism of, 145-72

*see also* individual electrolytes

Emotion

circulation and, 375-76

cortical centers for, 430, 446-47

gastric secretion and, 215

hypothalamic lesions and, 449-50

kidney function and, 381

menstrual cycle and, 543

physiological effects of, 456-57

Endocrine glands, *see* specific glands

Energy metabolism, 289-307

oxygen consumption and, 289

Enterogastrone, gastric secretion inhibition and, 212-13

Enzymes

bone and, 102-5, 107

genes and, 50-51

intracellular, tissue metabolism and, 303-5

neoplastic growth and, 90

radiation and, 30-32

*see also* individual enzymes

Epilepsy, 431-32

antiepileptic drugs, 432

emotional responses in, 430

Epinephrine

blood volume and, 327

gastric secretion and, 208

- Epinephrine (*cont.*)  
 gastrointestinal motility and, 223  
 heart and, 356-57  
 kidney circulation and, 382  
 norepinephrine and, 330-31, 455  
 pituitary hormone release and, 504-5  
 pulmonary circulation and, 184  
 synaptic transmission and, 452
- Ergonovine, heart and, 358-59
- Ergot, hypertension and, 389
- Estrogens, 546, 547-48  
 bone and, 110-11  
 gonadotropic potency and, 506  
 male accessories and, 547-48  
 mammary gland and, 549  
 ovulation and, 543  
 secretion of, 547-48  
 thrombocytopenia and, 251
- Ether, gastric secretion and, 209
- Eugenol, gastric mucus membrane and, 215
- Exercise, *see* Muscular exercise
- Eye  
 movements of, 492  
 nerve fibers of, polarization in, 490-91  
 radiotherapy and, 39  
 retina, *see* Retina  
*see also* Retina and Vision
- F**
- Fat  
 in diet  
 kidney function and, 385-86  
 metabolic functions and, 294  
 metabolism of  
 adrenocorticotrophic hormone and, 515-16  
 insulin and, 522-23
- Fatigue, heat and, 127
- Fertility, 541  
 radiation and, 35-37
- Fertilization, 545  
 of eggs, site of, 542
- Fetus  
 amino acid concentration in, 78  
 dicumarol therapy and, 246  
 hemoglobin of, 270  
 sex diagnosis of, 544
- Fever  
 alkalosis, respiratory, and, 269  
 brain metabolism and, 134  
 hypothalamic lesions and, 133  
 mechanism of, 135, 137
- Fibrillization, *see* Cells, fibrillization
- Fibrinogen, 254-55  
 calcium and, 254  
 sulfhydryl groups and, 254
- Fibrinolysin, 254-55

- Fitness, physical, oxyhemoglobin reduction as test of, 278-79
- Fluorine, bone and, 106
- Folic acid, radiation anemia and, 34
- Food intake, temperature regulation and, 124, 140
- Formaldehyde, mutagenic properties of, 48
- Fructose, sperm metabolism of, 539-40

**G**

- Gall bladder  
 disease of, secretin test, 229  
 intestinal absorption and, 226
- Gastrin, 209-10
- Genes  
 biosynthesis and, 53-57  
 enzyme control by, 50-51  
 pigmentation and, 51-52, 53
- Genetics, 47-67  
 of bacteria, 57-61  
 of cancer, 47  
*see also* Mutations
- Glucose  
 of blood  
 arterial pressure and, 121  
 body temperature and, 121  
 kidney and, 380  
 gastric secretion and, 208  
 oxidation of, insulin and, 521-22
- Glutamic acid, growth and, 80
- Glutathione, diabetes and, 520
- Glycine, hemoglobin formation and, 268
- Glycogen, in liver, hypothermia and, 128
- Glycolysis  
 in bone marrow  
 pH and, 301-2  
 respiration and, 302  
 in brain, enzymes and, 304
- Gonadotropins, hypophyseal, 549  
 adrenocorticotrophic hormone output and, 507  
 inanition and, 506-7  
 luteinizing hormone, 504, 549  
 ovulation and, 504, 543
- Gonads  
 adrenal cortex and, 510-11  
 metabolism and, 296
- Gout, adrenocorticotrophic hormone and, 518
- Gramicidin, peptide nature of, 83
- Gravity  
 circulatory effects, 316-17  
 tolerance to, 317
- Growth, 71-93  
 anoxia resistance changes in, 187-88  
 extracellular fluid changes in, 152-53  
 glutamic acid and, 80

Growth (*cont.*)

- growth hormone and, 86-87
- inhibition of, amino acids and, 82-84
- protein metabolism and, 71-93
- radiation and, 32

## Growth, neoplastic

- enzymes and, 90-91
- guanine synthesis in, 92
- protein composition of, 91
- protein metabolism and, 89-93
- see also* Cancer and Tumors

**H**

## Hair

- graying of, radiation and, 39
- growth of, adrenal cortical hormones and, 515

## Healing process, radiation and, 39

## Heart, 345-63

- arrhythmias of, 356-57
- beat, dynamics of, 345-52
- circulation, *see* Heart, coronary circulation
- congestive failure of
  - edema in, 161-66
    - renal circulation and, 323
    - kidney function and, 161-66
    - sodium retention and, 162
- coronary circulation, 357-59
  - drugs and, 358-59
  - nervous control of, 358-59
  - tests, 358-59
- coronary occlusion, ventricular fibrillation and, 358
- cycle
  - disease of heart and, 345-46
  - measurement of, 348
  - timing of, 345-46
- dilatation of, aminophyllin and, 272
- disease of, kidney function and, 374-76
- drugs and, 356-57
- edema in disease of, *see* Heart, congestive failure
- electrocardiography
  - intracardiac, 362-63
  - methods, 361-63
  - posture and, 363
  - T-wave, body temperature and, 129
- metabolism of, 359-60
  - lactate in, 359
  - pyruvate in, 359
  - succinate and, 299-300
- muscle, *see* Muscle, cardiac
- nerve conduction in, 401 (footnote)
- nervous control of, 352, 354
- output, *see* Cardiac output
- pressures in, 346-48
  - atrial fibrillation and, 346

Heart (*cont.*)

- pressures in (*cont.*)
  - comparative, 346-48
  - heart defects and, 347
  - quinidine and, 347
- rate
  - adenosinetriphosphate and, 353-54
  - exercise and, 355
  - heat stress and, 125
  - hypothermia and, 122-23, 458
    - atropine and, 123
    - vagotomy and, 123
  - norepinephrine and, 352
  - posture and, 355
  - temperature and, 355
  - reflexes, 352-53, 457, 458
  - size of, 351-52
  - stroke volume, measurement of, 349
  - vitamin deficiency and, 359-60

Heat, *see* Temperature

## Hemoglobin

- fetal, 270
- formation of, glycine and, 268
- gas transport and, 267-70
- hemoglobinuria, 380
- measurement of, 267-68
- oxyhemoglobin reduction time, physical fitness and, 278-79

## Hemophilia, 250

- blood clotting and, 238-39, 242-43
- thromboplastic activity and, 250

## Hemorrhage

- radiation and, 34
- shock, 328-29
  - transfusions and, 328

## Hemostasis, 237-38

- vasomotor phenomena and, 237-38
- serotonin and, 238
- see also* Blood clotting

## Heparin

- in blood, protamine titration test, 253
- blood clotting and, 252-53
- platelet agglutination and, 251

## Hibernation, cold adaptation and, 122

## Histamine

- blood flow and, 332
- gastric secretion and, 208-9, 210-11
- peptic ulcer and, 217-18
- pituitary hormone secretion and, 505
- pulmonary circulation and, 184
- radiation sickness and, 38

## Histidine, bacterial genetics and, 60

- Hodgkin's disease, cytoplasm in, 10
- Homeothermy, concept of, 128

## Hormones, 503-30

- absorption and, 226
- bone and, 108-12
- see also* individual hormones

## Humidity, skin humidity and, 154

- Hunger, 205-6  
 olfactory thresholds and, 206
- Hydargine, hypertension and, 389
- Hydrochloric acid  
 in stomach, 206-14  
 peptic ulcer and, 217, 219  
*see also* Stomach, hydrochloric acid  
 production of
- Hydrogen ion concentration  
 bone development and, 102  
 brain tissue respiration and, 302-3  
 glycolysis and, 301-2  
 tissue metabolism and, 301-3
- Hyperemia  
 drugs and, 377  
 kidney plasma flow and, 377
- Hypertension, *see* Kidney, pressor substances
- Hypertension, 332-35  
 adrenal gland and, 332, 387-88  
 desoxycorticosterone acetate and, 332-33, 387-88  
 drugs and, 389  
 hypertensin and, 386-87  
 kidney and, 333-34, 386-91  
 kidney damage in, 389-90  
 reflex responses and, 451  
 vasoexcitor material and, 387  
*see also* Arterial pressure
- Hypoglycemia, *see* Glucose, of blood
- Hypothalamus  
 emotion and, 449-50  
 heat regulation and, 449  
 ovulation and, 433  
 reproductive system and, 503-4  
 sleep and, 450  
 temperature regulation and, 133-35, 138, 141-42, 297  
 water balance and, 433
- Hypothermia, *see* Temperature, body
- I**
- Inanition  
 basal metabolism and, 292  
 extracellular fluid expansion and, 153  
 metabolism and, 294-95  
 pituitary hormone secretion and, 506-7  
 water distribution and, 168
- Infancy  
 kidney function in, 369-70  
 premature, edema of, 167
- Insemination, artificial, 537-39
- Insulin  
 adrenal cortical hormones and, 521  
 hexokinase and, 521-22  
 inactivation in body, 523-24  
 mechanism of action, 521-23  
 membrane permeability and, 522  
 pitressin, similarities to, 523
- Intestine, large, *see* Colon and Rectum
- Intestine, small  
 absorption by, 226-27  
 gall bladder and, 226  
 hormones and, 226  
 of vitamin A, 226  
 vitamins and, 226  
 motility of, 222-26  
 antihistamine drugs and, 224-25  
 atropine and, 222-23, 224  
 cerebral cortex and, 448  
 epinephrine and, 223  
 morphine and, 224  
 syntropan and, 222-23  
 tetraethylammonium and, 224, 226  
 radiation and, 38-39  
 reflexes of, 459-60
- Intracellular fluid, potassium and, 171
- Inulin, extracellular fluid measurement and, 151-52
- Ions, transport of, 146
- K**
- Ketone bodies, in blood  
 adrenal cortical hormones and, 515-16  
 exercise and, 293
- Kidney, 369-92  
 alcohol and, 385  
 antidiuretic hormone, *see* Pituitary, posterior  
 anuria, treatment of, 391-92  
 blood flow in, 322-23, 382-84  
 cardiac edema and, 323  
 epinephrine and, 382  
 exercise and, 373-74  
 nerve supply and, 382-83  
 shock and, 377-79, 382-83  
 shunts of, 382-83, 385  
 tubular reabsorption of water and, 163-64  
 blood glucose and, 380  
 clearance of, 370-77  
 diodrast, 370-71, 372-73  
 p-aminohippurate, 373-74, 382-83  
 tritacin, 370-71  
 cortex, necrosis of, 384  
 sickle cell anemia and, 384  
 development of, 369-70  
 diuresis, 155-60  
 cardiac edema and, 164  
 cold and, pitressin and, 124  
 drug actions on, 157  
 liver disease and, 157  
 solutes and, 158-60  
*see also* Kidney, water diuresis  
 excretion of, 371-72  
 chloride, 155  
 phosphate, parathyroid and, 529

Kidney (*cont.*)excretion of (*cont.*)

- proteins, exercise and, 374
- sodium, 155

## function of

- abdominal compression and, 376-77
- adrenal cortical hormones and, 157-58

## adrenal gland and, 384

## cold pressor test, 376

## dehydration and, 168

## fat in diet and, 385-86

## oxygen consumption and, 376-77, 379

## posterior pituitary and, 155-57

## pregnancy toxemia and, 385

## shock and, anoxia and, 378

## sodium and, in edema, 161-66

## glomerular filtration

## cardiac edema and, 162-64

## heart disease and, 374-76

## glycosuria, 380

## hemoglobinuria, 380

## hypertension and, 333-34, 386-91

## hypertension, hemorrhagic and, 329

## ischemia, 379-80

## metabolism of, 306-7

## enzymes and, 307

## succinate and, 299-300

## nephritis, 384-86

## nephrosis, 384-86

## oxygen consumption in, 273

## pathology of, nervous system and, 462

## plasma flow in, 373

## heart disease and, 374-76

## pressor substances, hypertension and, 386-87, 389

## size of, cerebral cortex and, 448

## tubular reabsorption

antidiuretic hormone and, *see* Pituitary, posterior

## diuresis and, 158

## heart disease and, 374-75

## hormones and, 164

## oxygen and, 163-64

## renal circulation and, 163-64

## of sodium, 372-73

## sodium and, in heart failure, 158-59

## of water, 158-59, 163-64, 372-73

## tubular secretion

of *p*-aminohippurate, salyrgan and, 371

## of potassium, 371-72

## tubular transport mechanism, 371

## vasoconstriction in, 458-59

## shock and, 377-78

## water diuresis

## antidiuretic hormone and, 381-82

## emotional stress and, 381

## Krebs cycle, tricarboxylic acid, 306

## L

## Labyrinth, vestibular nerves, rotational responses in, 451

## Lactate

- accumulation of, altitude and, 276
- heart metabolism and, 359

## Lactation, 549-50

## androgens and, 548

## pregnancy and, 550

## prolactin and, 549

*see also* Mammary glandLactic acid, *see* Lactate

## Learning

- cerebral mechanisms in, 425

- in spinal cord, 436

## Liver

- circulation in, 322

## disease of

- blood clotting and, 252

- phosphatase and, 220

- steroid production and, 511

- fat accumulation in, adrenocorticotrophic hormone and, 515-16

- glycogen in, hypothermia and, 123

- hemorrhagic hypertension and, 329

## injury to

- prothrombin and, 240, 245

- radiation and, 38

- insulin destroying activity of, 523

## metabolism of

- carcinogens and, 91-92

- succinate and, 299-300

- osmotic system of, 13-14

- oxidation in, 306-7

- oxygen consumption in, 272

- progesterone binding function, 547

- regeneration of, thyroxine and, 528

- secretion of, secretin and, 220

- thyroid hormone destruction in, 527

- vitamin D and, 108

- vitamins in, hypothermia and, 121-22

## Lungs

- diphosphopyridine nucleotidase in, 304

## edema of, 193

## embolism of, 193

- oxygen gradient in, 265-67

- oxygen pressure and, 276

- pulmonary circulation, 184-85, 323, 348

- arterial pressure in, 184-85

- epinephrine and, 184

- histamine and, 184

- oxygen saturation and, 267

- pulmonary arterial pressure and,

- exercise and, 348

- volume of, 179-81

- measurement of, 180-81

- respiration and, 179-81

- Luteinizing hormone, *see* Gonadotropins, hypophyseal  
 Lymph, flow, sympathetic nervous system and, 455  
 Lymph nodes, radiation and, 35  
 Lymphatic system  
   radiation and, 33  
   lymphoid tissue, adrenocorticotrophic hormone and, 87-88

## M

- Malnutrition, *see* Inanition  
 Mammary gland  
   development of, 549  
   hormones and, 549  
   *see also* Lactation  
 Mannitol, extracellular fluid measurement and, 151  
 Mecholyl, *see* Acetylcholinesterase  
 Membranes, of cells  
   amino acid transport, 78-79  
   permeability of, 11-14  
     insulin and, 522  
     ion exchange and, 11-13  
     nonelectrolytes and, 13  
     phosphatase and, 12-13  
     water and, 13-14  
   transport through, 145-50  
     diffusion and, 146-47  
     growth and, 78-79  
 Menstruation, 543-44  
   emotional shock and, 543  
   toxin of, 544  
 Mesopallium, *see* Cerebral cortex  
 Metabolism  
   basal, *see* Basal metabolism  
   energy, *see* Energy metabolism  
   fat in diet and, 294  
   gonads and, 296  
   hormones and, 295-96  
   of protein, *see* Proteins  
   rate of  
     body temperature and, 297  
     body weight and, 290, 292  
     endocrine glands and, 297-98  
     exercise and, 292-93  
     temperature, environmental, and, 127  
     temperature regulation and, 136-37  
     thyroxine and, 527-28  
   starvation and, 294-95  
   of tissues, 298-307  
     distribution within cell, 305-7  
     enzymes and, 303-6  
     glycolysis, 304, 307  
     enzymes and, 307  
     mitochondria and, 305-6  
     oxidation, 306-7

- Metabolism (*cont.*)  
   of tissues (*cont.*)  
     oxygen tension and, 299-300  
     pH and, 301-3  
     potassium exchange and, 12  
     radiation and, 32  
     succinate and, 299-301  
     x-ray radiation and, 31  
 Methemoglobin, in blood, 268-69  
 anoxia and, 268-69  
 Methylene blue, altitude tolerance and, 188  
 Methylxanthine, prothrombin and, 246  
 Morphine  
   diuresis and, 157  
   gastric secretion and, 209  
   intestinal motility and, 224  
 Muscle, cardiac  
   acetylcholine and, 360  
   circulation in, 271-72  
   electrical properties, 360-61  
   innervation of, 454-55  
   oxygen utilization in, 272  
 Muscle, skeletal, contraction of, blood flow and, 318  
 Muscular exercise  
   heart rate and, 355  
   ketone bodies in blood and, 293  
   kidney function and, 373-74  
   metabolic rate and, 292-93  
   physiological effects of, 313-14  
   pulmonary arterial pressure and, 348  
   sweating and, 136  
   temperature regulation and, 136-38  
 Mustard gas, mutagenic properties of, 48  
 Mutations, 48-62  
   in bacteria, 49, 57-61  
   in bacteriophage, 61-62  
   biochemical detection of, 48-49  
   chemical mutagens, 48  
   induced, 52-53  
   in Paramecium, 64-65  
   radiation and, 48  
   spontaneous, 52-53  
     measurement of rate, 59-60  
   in viruses, 61-62  
   x-ray radiation and, 52-53  
   in yeast, 62-63  
 Myelinization, temperature regulation and, 134

## N

- Nembutal, gastric secretion and, 209  
 Neoplasms, *see* Cancer; Growth, neoplastic; and Tumors  
 Neosynephrine, heart and, 357  
 Nerve  
   accommodation phenomena in, 406

Nerve (*cont.*)

- action potentials in, 401-3, 406, 416
    - subliminal, 414-15
  - cells, structure of, 9
  - conduction in, 399-418
    - blocking and, 404
    - electrical phenomena of, 399-416
    - electrotonus, 402-4
    - hypothermia and, 122
    - injury and, 404
    - membranes and, 399-406
    - permeability and, 399-400
    - polarization and, 399-406
    - velocity of, 400-1
  - degeneration of, 438
  - electrical phenomena of, 399-418
    - electrotonus, 402-4
  - excitation of, 399-418
    - cathodal field and, 407-8
    - inhibition and, 411-13, 414-16
    - subliminal, 414-15
  - fibers
    - size differentiation, 409-10
    - structure of, 437-38
  - impulses
    - asynchronization of, 411-12
    - summation of, 408-10, 413
    - synchronization of, 409-12
  - inhibition of, 407-8, 411-18
    - disease and, 414
    - in Golgi cells, 416-17
    - summation and, 413
    - in two-neuron arc, 412-13, 416
  - membrane of
    - conduction and, 399-406
    - permeability of, 399-400
    - polarization and activity of, 399-406
    - regeneration of, 14
  - synaptic transmission, 407-18
    - drugs and, 452
- Nerves
- cardiac, action potential of, 354
  - chorda tympani, taste and, 471-72, 475
  - phrenic, respiratory reflexes and, 457
  - vagus
    - cardioaccelerator fibers in, 354
    - heart reflexes and, 353
    - stimulation of, heart action and, 455-56
  - vestibular, *see* Labyrinth
- Nervous system, central
- arcuate nucleus, taste and, 473-75
  - autonomic activity and, 445-62
  - frequency modulation of stimuli, 423-24
  - instability of, 422
  - mechanical analogies, 421-24
  - neural nets, 422
  - oxygen pressure and, 276

Nervous system, central (*cont.*)

- parainsular cortex, taste and, 474-75
  - respiration and, 181-82
  - somatic functions of, 421-38
  - sweating and, 451
  - vasomotor phenomena and, 451-52
  - visceral functions of, 445-62
  - vomiting and, 228
  - see also* Brain and Cerebral cortex
- Nervous system, visceral, 445-62
- drugs and, 461
  - synapses of, 454
  - see also* Autonomic nervous system and Sympathetic nervous system
- Niacin, heart metabolism and, 359-60
- Nicotinamide
- altitude tolerance and, 188
  - vision and, 487
- Nicotine
- diuresis and, 157
  - pituitary inhibition by, 157
- Nicotinic acid
- altitude tolerance and, 188
  - synthesis of, gene control of, 53-54
- Nitrogen
- excretion of, adrenalectomy and, 513-15
  - retention of, pituitary growth hormone and, 508
  - transport in blood, 278
- Norepinephrine
- heart rate and, 352
  - physiological effects of, 330-31
  - in vasomotor phenomena, 315
- Nutrition, reproduction and, 550-51

## O

- Obesity, temperature regulation and, 140
- Olfaction, *see* Smell
- Olfactory system, 476-81
- end organs of, 477-79
  - excitations of, 477
  - infrared radiation in, 477
  - respiration and, 478-79
  - nerve paths of, 479-81
  - receptor nerves of, 477-78
  - mechanical excitability of, 478-79
  - nontopographical organization of, 478
  - see also* Smell
- Osmotic pressure
- in cells, variations in, 149
  - of extracellular fluid, 149
  - kidney function and
    - hormone control and, 156
    - sodium concentration and, 156
- Osteogenin, bone growth and, 102
- Ovariectomy, androgens and, 548

Ovary, theca-cell tumors, estrogen secretion of, 547-48

Ovulation

- drugs and, 542-43
- hormones and, 542-43
- hypothalamus and, 433
- luteinizing hormone and, 504
- progesterone and, 542
- superovulation, 542
- time of, 541

Ovum, age of, sex of offspring and, 546

Oxygen

- consumption of
  - altitude and, 189
  - cardiac output and, 350
  - lobotomy and, 429
  - succinate and, 299-301
- deficiency of, *see* Oxygen deficiency
- excess of, respiration and, 190-91
- kidney function and, 379
- oxygen poisoning, 276
- respiration and, 182-191

Oxygen deficiency

- cardiac output and, 351
- circulation and, 329-30
- effects of, 192
- growth changes in resistance to, 187-88
- hypothermia and, 122

P

Pain, referred, 437

Pancreas

- disease of, 221-22
- diagnosis of, 221
- external secretion of, 220-22

Pantothenic acid

- adrenal compensation by, 513
- bone and, 107

Paramecium

- antigenic characters of, 65-67
- cytoplasm inheritance in, 63-67

Parathyroid gland, 528-30

- bone and, 109, 528-29
- phosphate excretion and, 29
- transplantation of, 85
- vitamin D and, 108-9

Parkinson's disease, *see* Brain, stem

Penicillin

- bacterial resistance to, 60, 78
- prothrombin and, 246

Pentobarbital, gastric secretion and, 209

Pentothal, sodium, hypothermia and, 123

Pepsin, secretion of, 214

Peptides, synthesis of, 73-77

- adenosinetriphosphate and, 75

Peripheral circulation, 311-35

- muscle contraction and, 318

Peripheral circulation (*cont.*)

- sympathetic nervous system and, 334-35

temperature and, 318-20

*see also* Arterial pressure, Blood flow, Capillaries, Vasomotor phenomena, etc.

Peritoneal cavity, pressure in, posture and, 228

Permeability, of cell membranes, *see* Membranes, of cells

Phlorizin, absorption and, 226

Phosphatase

- in bone, 102-4
- cell permeability and, 12-13
- liver disease and, 220
- osmosis and, 12-13

Phosphate, excretion of, parathyroid and, 529

Phosphomonoesterase, 107

Phosphorylation, of carbohydrate, potassium transport and, 147-48

Physiology, recent history of, 1-6

Pigmentation, genes and, 51-52, 53

Pitressin

- adrenal cortical hormone and, 158
- diabetes insipidus and, 158
- diuresis and, in cold stress, 124
- insulin, similarities to, 523
- see also* Pituitary, posterior, anti-diuretic hormone

Pituitary gland, radiation and, 36-37

Pituitary, anterior, 503-9

adrenocorticotrophic hormone

adrenal cortex metabolism and, 511-13

anaphylactic shock and, 519

bone growth and, 108

cartilage formation and, 108

diabetes and, 521

drugs and release of, 504-5

epinephrine and release of, 504-5

fat metabolism and, 515-16

gonadotropin production and, 507

hair growth and, 515

histamine and, 505

lymphoid tissue and, 87-88

protein metabolism and, 87-88

radiation and, 505

skin growth and, 515

growth hormone, 508-9

amino acids in blood and, 523

arginase and, 509

biochemical effects of, 86-87

bone growth and, 528

carcinogenesis and, 92-93

crystallization of, 85-86

diabetes and, 521

nitrogen retention and, 508

- Pituitary, anterior (*cont.*)  
  growth hormone (*cont.*)  
    physiological effects of, 86-87  
    protein metabolism and, 86-87, 509  
  insulin effects and, 522  
  luteinizing hormone, *see* Gonadotropins  
  hypophyseal  
  prolactin  
    estrogen and, 506  
    lactation and, 549  
  thyrotropic hormone, iodine uptake of  
    thyroid and, 524  
  tropic hormones, steroid production  
    and, 508
- Pituitary, posterior  
  alcohol as inhibitor, 157  
  antidiuretic hormone, 155-57, 158  
    renal tubular reabsorption and, 372  
    water diuresis and, 381-82  
  *see also* Pitressin  
  cold as inhibitor, 157  
  kidney function and, 155-57  
    osmosis and, 156  
  nicotine as inhibitor, 157
- Plasma  
  osmotic pressure of, edema and, 164-65  
  volume of  
    edema and, 164-65  
    measurement of, 326
- Platelets, blood, 250-52  
  agglutination of, 251  
  heparin and, 251  
  clot retraction and, 250  
  clotting and, 238-39, 249  
  thrombocytopenia  
    allergy and, 251  
    blood clotting and, 242-43  
    estrogens and, 251  
    thromboplastic activity test, 250  
    urethane and, 251
- Pneumococcal infections, adrenal extract  
  and, 519
- Polycythemia  
  altitude and, 275  
  red cell production and, 76
- Posture  
  arterial pressure and, 316-17  
  circulation time and, 324-25  
  electrocardiography and, 363  
  heart rate and, 355  
  intraperitoneal pressure and, 228  
  venous pressure and, 351  
  vital capacity and, 181-82
- Potassium  
  excretion of, 372  
  intracellular fluid and, 171  
  therapy, 148  
    sodium and, 148  
  transfer of, diabetes and, 148, 171
- Potassium (*cont.*)  
  transport of, 148-50  
    carbohydrate phosphorylation and,  
      147-48  
    sodium and, 148
- Pregnancy  
  cardiac output and, 350  
  diagnostic tests, 544  
  edema in, 167  
  toxemia of  
    blood pressure and, 388  
    kidney function and, 385
- Procaine  
  anuria and, 391-92  
  heart and, 356
- Progesterone, 546-47  
  hepatic binding of, 547  
  mammary gland and, 549  
  ovulation and, 542
- Prolactin, *see* Pituitary, anterior
- Protein hydrolysate, gastric secretion and,  
  211
- Proteins  
  in diet  
    adrenal cortex and, 513-15  
    animal protein factor, 81-82  
    antibody protein synthesis and, 80-  
      81  
    convalescence and, 295  
    pituitary growth hormone and, 509  
    reproduction and, 81-82, 550-51  
    specific dynamic action of, 294  
  dietary deficiency of  
    edema and, 166  
    overhydration and, 153  
  metabolism of  
    adrenal cortical extract and, 513-15  
    carcinogenesis and, 91  
    growth and, 71-93  
    hormones and, 86-89  
    measurement of, 72-73  
    in tumors, 90  
    *see also* Proteins, in diet  
  synthesis of, 73-77  
    nucleic acid and, 77
- Proteins, plasma  
  Ac-globulin, 239-43  
  albumin, blood clotting and, 253
- Prothrombin, 239-43  
  deficiency of, hypotherbinemia, con-  
    genital, 247  
  determination of, 243-45  
  dicumarol therapy and, 244-46  
  digitalis and, 246  
  liver damage and, 240  
  loss of, in stored plasma, 241-42  
  methylxanthines and, 246  
  penicillin and, 246  
  prothrombin clotting time, 244-45

- Prothrombin (*cont.*)  
 prothrombin clotting time (*cont.*)  
   determination of, 243-45  
   venom-lecithin test, 245  
 sulfaquinolaxine and, 246  
 sulfathiazole and, 246  
 tromexan and, 246  
 vitamin A excess and, 246  
 vitamin K and, 247
- Protoplasm  
 birefringence of, 9  
 consistency of, 8  
 physical properties of, 7-23  
 sol-gel transformation of, 8-9, 21-23  
 structure of, 9  
 ultraviolet radiation and, 7-8, 10  
 viscosity of, 8  
 zeta potentials, 9
- Pulmonary circulation, *see* Lungs, pulmonary circulation
- Pyrogens  
 fever and, 133, 134, 135, 137  
 peptic ulcer and, 218
- Pyruvate, heart metabolism and, 359
- R**
- Radiation, 27-40  
 adrenal cortex and, 37  
 assimilation and, 32  
 bacteriophage and, 31  
 blood and, 32-34  
 blood clotting and, 33  
 bone growth and, 39  
 bone marrow and, 33-34  
 brain and, 39  
 digestive organs and, 38-39  
 enzyme inhibition by, 30-32  
 eye and, 39  
 fertility and, 35-37  
 folic acid and, 34  
 growth and, 32  
 hair graying and, 39  
 healing process and, 39  
 hemorrhage and, 34  
 ionizing effects of, 30-31  
 liver damage and, 38  
 lymphoid tissue and, 33, 35  
 mammals, effects on, 27-28, 32-40  
 measurement of, 29-30  
 mutations and, 48  
 pituitary gland and, 36-37, 505  
 radioactive waste disposal, 28  
 red blood cells and, 33-35  
 reproductive organs and, 35-37  
 rutin and, 34  
 safeguards in use of, 28-29  
 sickness, 37-39  
 desoxycorticosterone acetate and, 38

- Radiation (*cont.*)  
 sickness (*cont.*)  
   histamine and, 38  
   vitamins and, 38  
   water balance and, 37-38  
   thymus and, 35
- Radiation, infrared  
 in olfactory excitation, 477  
 testis degeneration and, 540
- Radiation, microwave  
 hazards of, 29  
 testis degeneration and, 540
- Radiation, neutron, hazards of, 29
- Radiation, ultraviolet  
 bacterial mutations and, 60-61  
 bacteriophage mutations and, 62  
 protoplasm and, 7-8
- Radiation, x-ray  
 cell nucleus and, 10  
 hazards of, 29  
 metabolism and, 31  
 mutations and, 52-53  
 peptic ulcer and, 219
- Rectum, nerve coordination with anus, 225
- Red blood cells  
 altitude and, 187-88  
 erythropoiesis, anoxia as stimulant, 268  
 J substance in, 67  
 number of, viscosity and, 313  
 polycythemia, *see* Polycythemia  
 production of  
   anemia and, 76  
   polycythemia vera and, 76  
 volume of, measurement of, 326  
 x-ray radiation and, 33-35
- Reflex action, 456-61
- Reflexes  
 Bainbridge, 457  
 Hering-Breuer, *see* Respiration, respiratory reflexes  
 mirror image effect, 460-61  
 vascular, 457-59  
 visceral, 456-61
- Relaxin, 548
- Renin, hypertension and, 386-87, 389
- Reproduction, 537-51  
 altitude and, 541  
 protein in diet and, 81-82, 550-51  
 tropical climate and, 540  
 vitamins and, 550-51
- Reproductive behavior, 541
- Reproductive system  
 cholesterol storage, gonadotropins and, 507-8  
 hypothalamus and, 503-4  
 radiation and, 35-37  
 vascular patterns of, 543
- Respiration, 179-93

Respiration (*cont.*)

- acid-base balance and, 182-83
  - altitude and, 186-90
  - alveolar air
    - altitude and, 188-89
    - composition of, 183-84
    - measurement of, 265-67
    - oxygen saturation of blood and, 266
    - pentothal anesthesia and, 183
  - alveolar pressure and, 188-89
  - alveolar-arterial equilibrium, 265-67
  - apnea, 182
    - gas exchange during, 277
    - veratridine and, 182
  - artificial, methods of, 191-92, 277
  - carbon dioxide and, 182-83, 185-86
  - cardiac output and, 349-50
  - cerebral cortex and, 429, 447
  - chemical regulation of, 182-83
  - glycolysis and, 302
  - heat stress and, 125
  - lung volume and, 179-81
  - mechanism of, 179-92
  - nervous regulation of, 181-82
  - olfactory excitation and, 478-79
  - of organs, *see* specific organ
  - oxygen poisoning and, 190-91
  - oxygen tension and, 182-83
    - altitude and, 188, 190
  - pressure breathing, 189-90
    - altitude and, 189-90
    - blood volume and, 328
  - pulmonary ventilation, basal metabolism and, 292
  - respiratory reflexes, 457-58
    - barbiturates and, 181
    - Hering-Breuer reflex, 181-82
    - phrenic nerve and, 457
  - vital capacity
    - body position and, 181-82
    - lung volume and, 180-81
  - water loss in, 188-89
- Resuscitation, 191-92
- Retina
- action potential of, 495, 499
  - carotid sinus and, 458
  - electrical responses of, 490-92
  - electroretinography, 494-95
    - diagnostic use of, 494
  - elements of, 490-93, 499-500
  - emotional stress and, 457
  - pigments of, 488-89
- Retinene, vitamin A and, 486-87, 488
- Rheumatic fever, adrenal cortical hormones (Compound E) and, 517
- Riboflavin
  - bone and, 107
  - cartilage and, 107
- Rickets, 106-8

Rickets (*cont.*)

- diet and, 106
  - osteopetrosis in, 107
  - vitamin D and, 107
- Rutin, radiation and, 34

## S

- Salicylates, prothrombin and, 246
- Salt
  - deficiency of, circulation and, 169
  - see also* Chloride and Sodium
- Salyrgan, renal tubular secretion and, 371
- Scurvy, capillary tests, 324
- Seconal, arterial pressure and, 334
- Secretin
  - gall bladder disease test, 229
  - liver stimulation by, 220
  - pancreatic enzymes and, 221
  - pancreatitis diagnosis and, 221
- Semen
  - citric acid in, 540
  - fructolysis in, 539-40
- Sensations, cutaneous, temperature regulation and, 131-32
- Serotonin, 238
- Sex, differentiation
  - age of egg and, 546
  - age of sperm and, 546
  - environmental factors and, 545-46
- Sex hormones, bone growth and, 110-12
- Shock, 328-29
  - kidney blood flow and, 377-79, 382-83
- Shock therapy, electric, autonomic reflexes and, 450
- Skin
  - blood vessels of, hormones and, 544
  - growth of, adrenal cortical hormones and, 515
  - humidity of
    - air humidity and, 154
    - temperature and, 154
  - temperature of
    - blood flow and, 129-30, 319
    - comfort and, 129, 132-33
    - heat stress and, 125
    - temperature regulation and, 132, 138
- Sleep, hypothalamus and, 450
- Smell, 476-81
  - hippocampus and, 480-81
  - thresholds of,
    - appetite and, 476-77
    - hunger and, 206
    - satiety and, 476-77
  - see also* Olfactory system
- Sodium
  - acidosis and, 170
  - cardiac edema and 161-66
  - deficiency of, circulation and, 169-70

Sodium (*cont.*)

- diarrhea and, 170
- edema and, 161-66, 169-70
- excretion of, 157-59
  - adrenal cortex and, 154-55, 157
  - heart failure and, 161-63
- extracellular fluid measurement and, 151-52
- kidney function and, 156
- renal tubular absorption of, 372-73
- transport of, 147, 149-50
  - potassium and, 148
- Spasm, suppressor system and, 435
- Specific dynamic action
  - of amino acids, 293
  - of carbohydrates, 294
  - of proteins, 294
- Speech, cerebral cortex and, 424-25
- Spermatogenesis, radiation and, 36
- Spermatozoa
  - age of, sex of offspring and, 546
  - metabolism of, 539-40
  - oxidation of, 539
  - thyroxine and, 539
- Spinal cord, 436-37, 451-52
  - hypertension and, 451
  - learning in, 436
  - Porter phenomenon, 437
- Starvation, *see* Inanition
- Steroid hormones, 546
  - ascorbic acid and, 513
  - pituitary hormones and production of, 508
  - site of production, 509-11
- Steroids, liver and, 88
- Stomach
  - absorption by, 226-27
    - hormones and, 226
    - of vitamin A, 226
    - vitamins and, 226
  - acidity of, lobotomy and, 429
  - blood flow in, 227
  - cancer of, adrenal cortical extract and, 514
  - electric potentials of, 207-8
  - emptying time of
    - doryl and, 216
    - drugs and, 223-24
    - urecholine and, 216
  - hunger contractions of, 205
  - vagotomy and, 205
  - hydrochloric acid production of, 206-14
    - carbonic anhydrase and, 207
    - drugs and, 209
    - electric potential of stomach wall and, 207-8
    - epinephrine and, 208
    - gastrin and, 209-10

Stomach (*cont.*)

- hydrochloric acid production of (*cont.*)
  - glucose and, 208
  - histamine and, 208-9, 210-11
  - oxidation and, 207
  - sulfonamides and, 208
  - see also* Stomach, secretion of
- innervation of, 459
- motility of, 222-26, 459-60
  - cerebral cortex and, 448
  - epinephrine, and 223
  - syntropan and, 222-23
  - tetraethylammonium and, 213
  - urecholine and, 223
  - vagotomy and, 216
- mucus membrane of, eugenol and, 215
- mucus secretion in, 214-15
- radiation and, 39
- reflexes of, 459-60
- secretion of, 206-216
  - acetylcholine and, 209-10
  - antihistamine drugs and, 213-14
  - benadryl and, 211
  - emotional stress and, 215
  - inhibition of, 211-14
  - mecholy and, 210
  - nocturnal, 219
  - peptic ulcer and, 219
  - see also* Stomach, hydrochloric acid production of
- Streptomycin, bacterial resistance to, 59-60
- Submarine physiology, respiration, 185-86, 190-91
- Succinate
  - oxidation of, 299-301
  - tissue metabolism and, 299-301
  - oxygen tension, and 299-300
- Sulfaquinoxaline, prothrombin and, 246
- Sulfathiazole, prothrombin and, 246
- Sulfhydryl compounds
  - diabetes and, 519-20
  - fibrinogen and, 254
- Sulfonamides
  - bone and, 103
  - gastric secretion and, 208
- Surface area, basal metabolism and, 296-98
- Sweat
  - composition of, adrenal cortex and, 155
  - electrolyte loss in, 154-55
  - water loss in, 154-55
- Sweating
  - central nervous system and, 451
  - chloride loss in, 127
  - creatinine loss in, 127
  - heat stress and, 126
  - rate of, 139
  - heat stress and, 137

- Sweating (*cont.*)  
   rate of (*cont.*)  
     work and, 136-37  
     threshold, 139  
 Sympathetic nervous system, 445-62  
   lymph drainage and, 455  
   peripheral circulation and, 334-35  
   stimulation of, 453-54  
   sympathectomy  
     reflex phenomena after, 453  
     vasomotor phenomena after, 453  
     vasomotor phenomena and, 316  
   *see also* Autonomic nervous system  
 Syntropan, gastrointestinal motility and, 222-23

## T

- Taste, 469-75  
   buds  
     development of, 471-72  
     excitation of, 472  
     number of, 471-72  
   cortical receptive area for, 474  
   end organs, nongustatory, 472  
   indices, 470  
   nerve paths of, 473-75  
   nerves of, 471-72  
     chorda tympani, 471-72, 475  
     parainsular cortex and, 474-75  
     preference thresholds, 471  
     submodalities of, 472-73  
     "taste blindness," 470-471  
     diabetes and, 470-71  
   thresholds of, 469-71  
     alkaline, 470  
     regional variations in, 470  
     sex differences in, 470  
     smoking and, 470  
 Teeth  
   phosphatase in, 103-4  
   vitamin C and, 107  
 Temperature, body, 119-41  
   altitude and, 189  
   arterial pressure and, 121  
   blood sugar level and, 121  
   blood temperature and, 128-29, 319-20  
   fever, *see* Fever  
   heart and, T-wave, 129  
   heat and, 125-26  
   heat loss, 139-40, 297  
     from feet, 139-40  
     measurement of, 119-20  
   hypothermia, 121-23  
     anoxia and, 122  
     heart rate and, 122-23  
     liver and, 121  
     nerve conduction and, 122  
     pentothal anesthesia and, 123  
   Temperature, body (*cont.*)  
     metabolic rate and, 297  
     regulation of, 133-41, 296-98  
       anesthesia and, 138  
       arterial pressure and, 134  
       brain metabolism and, 134-35  
       central nervous system and, 133-35, 138-39  
       cholinesterase and, 135  
       food intake and, 124, 140  
       hypothalamus and, 297, 449  
       myelination and, 134  
       nervous system and, 133-35, 138-39  
       obesity and, 140  
       peripheral mechanism of, 123-28, 133-34, 136-40  
       pyrogens and, 135, 137-38  
       skin temperature and, 132  
       sweating and, 136-37, 139  
       thermal sensation and, 131-32  
       vasomotor phenomena and, 129-32, 134, 137  
       work and, 136-38  
   skin temperature, *see* Skin, temperature of  
   sweating, *see* Sweating  
   thermal balance and, 124-25, 132  
   thermal interchange and, 128  
   water loss, measurement of, 120  
 Temperature, environmental  
   adaptation to, 121-27, 167, 291-92  
   basal metabolism and, 291-92  
   blood flow and, 318-19  
   cardiac output and, 355  
   cold, 123-25  
     adaptation to, 122, 124  
     hibernation and, 122  
     heart rate and, 458  
     metabolic rate and, 123-24  
     pituitary inhibition by, 157  
     response to, 121-25  
   cold injury, therapy for, 125  
   cold stress  
     clothing and, 124-25  
     diet and, 124  
     diuresis in, pitressin and, 124  
     thermal balance and, 124-25  
     wind and, 124  
   comfort and, 129, 132-33  
   heart rate and, 355  
   heat, 125-28  
     adaptation to, 126-27  
     fatigue and, 127  
   heat stress  
     arterial pressure in, 125  
     basal metabolism and, 296-98  
     body temperature and, 125-26  
     dehydration and, 126  
     heart rate in, 125

- Temperature, environmental (*cont.*)  
 heat stress (*cont.*)  
   respiration in, 125  
   skin temperature in, 125  
   sweating and, 126, 137  
   tolerance to, 125  
   tolerance time, 126  
 physiological responses to, 119-41  
 radiation and, measurement of, 120-21  
 reproduction and, 540  
 skin humidity and, 154  
 temperature regulation and, *see* Temperature, body, regulation of  
 thermal balance and, 124-25, 132  
 water loss and, 167
- Testis  
 cyclic changes in, 540  
 radiation and, 540
- Testosterone  
 arginase and, 509  
 protein metabolism and, 88
- Tetraethylammonium salts  
 arterial pressure and, 388  
 blood flow and, 331, 334-35  
 intestinal motility and, 224, 226  
 stomach emptying and, 223  
 stomach motility and, 213
- Thalamus  
 cortical electrical activity and, 433  
 functions of, 432-33  
 thalamic syndrome, 433  
*see also* Brain, diencephalon
- Theophylline, mutagenic properties of, 48
- Thiocyanate  
 antithyroid effect of, 525  
 extracellular fluid measurement and, 153-54  
 gastric secretion and, 208
- Thirst, 160-61  
 salivary glands and, 161
- Thrombocytopenia, *see* Platelets, blood
- Thromboplastic substances  
 activity of, test, 250  
 blood clotting and, 248-49
- Thymus, radiation and, 35
- Thyroid gland, 524-28  
 basal metabolism and, 295-96  
 bone and, 109, 111  
 colloid droplet formation in, 524-25  
 diiodotyrosine formation in, 525  
 extract of, absorption and, 226  
 hormone of  
   action of, 526  
   hepatic destruction of, 527  
   distribution of, 527  
   nature of, 526-28  
   tissue reactions of, 527  
*see also* Thyroxine  
 iodine metabolism of, 524-27
- Thyroid gland (*cont.*)  
 iodine metabolism of (*cont.*)  
   pituitary hormone and, 524  
   thiocyanate and, 525  
   thyrotropic hormone, *see* Pituitary, anterior  
   thyroxine formation in, 525  
   vitamin A and, 527
- Thyroxine  
 excretion of, 527  
 formation of, 525  
 liver regeneration and, 528  
 metabolic rate and, 527-28  
 pituitary hormone secretion and, 506  
 sperm metabolism and, 539  
*see also* Thyroid gland, hormone of
- Tobacco smoking, taste thresholds and, 470
- Tourniquets, reflexes and, 461
- Transplantation, of parathyroid gland, 85
- Tremor, 433-35
- Triticin, kidney clearance of, 370-71
- Tromexan, prothrombin and, 246
- Tryptophane, synthesis of, gene control of, 53-54
- Tumor, brain, cerebral circulation and, 321
- Tumors, protein metabolism in, 90

## U

- Ulcer, peptic, 216-19  
 cinchophen and, 218  
 histamine and, 217-18  
 hydrochloric acid and, 217, 219  
 nocturnal gastric secretion and, 219  
 pyrogens and, 218  
 x-ray radiation and, 219
- Ultraviolet radiation, *see* Radiation, ultraviolet
- Umbilical cord, blood flow in, 322
- Urea cycle, amino acids in, 77
- Urecholine  
 gastric motility and, 216, 223  
 gastric retention and, 216
- Urethane  
 mutagenic properties of, 48  
 thrombocytopenia and, 251
- Urine  
 composition of, 156-61  
 volume of, solutes and, 159-60
- Urogastrone, gastric secretion inhibition and, 212-13

## V

- Vagotomy  
 digestion and, 215-16  
 gastric hunger contractions and, 205

- Vagotomy (*cont.*)  
 heart rate in hypothermia and, 123  
 Vagus nerve, *see* Nerves, vagus
- Vasomotor phenomena  
 antihistamine drugs and, 316  
 arterial pressure and, 314-16  
 carotid sinus and, 314  
 central nervous system and, 451-52  
 circulation control by, 314-16  
 cold and, 319-20  
 in diabetic coma, 320  
 exercise and, 314, 318  
 hemostasis and, 237-38  
 norepinephrine and, 315  
 oxygen intake and, 329-30  
 saline injections and, 315  
 sympathectomy and, 453  
 sympathetic nervous system and, 316  
 temperature and, *see* Temperature,  
 body, temperature regulation  
 vasopressor reflex, 458  
*see also* Arterial pressure, Blood flow,  
 etc.
- Veins  
 circulation in, 324  
 varicose, venal circulation and, 324  
*see also* Venous pressure
- Venom-leithin test, for prothrombin clot-  
 ting time, 245
- Venous pressure, 351  
 measurement of, 311-12  
 posture and, 351
- Veratridine, apnea and, 182
- Viruses, genetics of, 60-61
- Vision, 485-500  
 cerebellar lesions and, 436  
 color vision, 492-93, 500  
 brightness and, 496  
 color blindness, 497-99  
 deuteranopic vision, 497  
 dominator activity and, 496-97  
 impulse frequency and, 493  
 inhibition and, 497  
 luminosity and, 496-97  
 polychromatic theory of, 496  
 protanopic vision, 497  
 wave lengths and, 496  
 dark adaptation, 488-89, 493, 494-95  
 on/off elements and, 488  
 distance evaluation, 499  
 electrical responses of retina, 490-92  
 eye movements, *see* Eye, movements of  
 light adaptation, 492, 494-95  
 neurological mechanism in, 490-93, 495,  
 498-500  
 off/on ratio, 491-93  
 on/off elements, 488, 490-93  
 polarity of, 490-91  
 photochemical processes in, 486-89
- Vision (*cont.*)  
 pupillary reflexes, 495  
 quantum theory of, 498-99  
 retinene and, 486-87  
 stereoscopic effects, 499  
 threshold phenomena of, 498-99  
 visual pigments, *see* Retina, pigments of  
*and* Visual purple  
 vitamin A and, 486-87, 488  
 vitamin E and, 487  
 wave length discrimination, 492-94
- Visual purple, 487-89, 494  
 bleaching process of, 488-89  
 breakdown of, 487, 488-89  
 temperature and, 489  
*see also* Retina, pigments of
- Vital capacity, *see* Respiration
- Vitamin A  
 absorption of, 226  
 bone and, 107  
 deficiency, reproduction and, 550-51  
 excess, prothrombin and, 246  
 thyroid atrophy and, 527  
 vision and, 486-87, 488
- Vitamin B complex  
 bone and, 107  
 deficiency, absorption and, 226  
 radiation sickness and, 38  
 reproduction and, 550
- Vitamin C  
 bone and, 107  
 deficiency, bone and, 104, 107, 111  
 teeth and, 107  
*see also* Ascorbic acid
- Vitamin D  
 bone and, 107, 108  
 liver and, 108  
 parathyroid gland and, 108-9  
 rickets and, 106-8
- Vitamin E., vision and, 487
- Vitamin K  
 deficiency, dicumarol therapy and, 245-  
 46  
 prothrombin and, 247
- Vitamins, absorption and, 226
- Vomiting, central nervous system and, 228

## W

- Water  
 balance  
 hypothalamus and, 433  
 radiation and, 37-38  
 body weight and, 151-52  
 distribution of, 145-54  
 dehydration and, 168  
 diarrhea and, 170  
 measurement of, 150-51  
 pathological variations of, 171

Water (*cont.*)

- distribution of (*cont.*)
  - salt and, 169
  - starvation and, 168
- excesses of
  - malnutrition and, 153
  - protein depletion and, 153
- exchanges of, 154-61
  - in dehydration, 167-68
- excretion of
  - by kidneys, 155-60
  - in respiration, 188-89
  - see also* Kidney, function of
- extracellular
  - edema and, 164-66
  - growth changes in, 152-53
  - measurement of, 151-53
- heavy, *see* Deuterium oxide

Water (*cont.*)

- loss
    - environmental temperature and, 167-68
    - insensible, 154
    - respiratory, 154
    - in sweat, 154-55
  - measurement of, 150-54
  - metabolism of, 145-72
  - transfer of, through membranes, 145-50
- Weight, body
- arterial pressure and, 313
  - basal metabolism and, 290, 292
  - water volume and, 151-52

## Y

- Yeast, mutations in, 62-63